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### THE CONTRIBUTIONS OF GREAT BRITAIN TO GYNECOLOGY AND OBSTETRICS

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THE history of medicine is fascinating. In 1921, Walter Chipman, our president, eloquently portrayed the progress of gynecology in this country. He referred to the influence of Great Britain and traced the establishment of our oldest medical schools and hospitals to some of those Americans who finished their education in the universities of Scotland or England.

Great Britain figured largely also in the development of gynecology and obstetrics. Her contributions were of the greatest value and these, in compliment to our distinguished guest, I have chosen as the subject of my address.

To begin with, we may regard gynecology with obstetrics as a most important specialty. Fairbairn in a delightful preface to his textbook says, "Although to the life and the health of the individual the reproduction function is not essential, it is the very source of the life of the nation: hence the communal and sociologic aspect is relatively much more prominent in these subjects than in the other branches of medical science."

William Harvey was the first English writer upon obstetrics, and William Giffard was the first to publish substantial contributions.

The invention of the forceps by the Chamberlens had much to do with the rise of the accoucher. Obstetrics as pointed out by Fairbairn

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grew up somewhat outside the field of medicine and surgery. When manuscripts upon obstetrics first appeared in English, they were considered objectionable reading for anyone but midwives. There was also great prejudice against male help in labor, and this arose from the fact that since men were summoned only in emergencies, the child or even the mother usually perished.

In 1760, Elizabeth Nihell, the great champion of the midwives in England, published *A Treatise on the Art of Midwifery*, setting forth the objections to male help in labor. She directed her denunciation largely against William Smellie who is credited with being the founder of modern obstetrics in England.

Smellie (1697-1763) in his epoch-making work cleared up many misconceptions and superstitions which still enshrouded the whole theory of the practice of midwifery.

William Hunter (1718-1783), another famous Scot, was a contemporary of Smellie's and the brother of John Hunter. His book, *The Anatomy of the Gravid Uterus* (1774), is declared by Cutter to be "one of the most remarkable productions of the eighteenth century."

Special mention must be made of Charles White of Manchester, who, in 1773, observed the incidence of puerperal sepsis in private practice and noticed its contagiousness. He advocated certain principles, among them being cleanliness, ventilation, and chloride of lime disinfection. His pupils, Kirkland (1776) and Gordon (1775), corroborated his views and equaled his results.

"The English obstetricians," said Adami, "first found control over puerperal fever; they held to the contagious theory of the origin of the disease, said the condition was preventable and so must be prevented." Later these principles were lost sight of by the English school and their subsequent revival resulted from the work of Holmes and Semmelweiss.

As we approach the year 1876 when this Society was founded, we enter the period of the greatest interest in the development of pelvic surgery. Here we encounter the men of Great Britain who left their indelible impress upon it, and especially Simpson, Wells, Lister, and Tait. Three of them were alive at that time. Simpson had died six years earlier, Wells had reached the age of fifty-eight, Lister was forty-nine, and Lawson Tait was thirty-one years old.

In estimating the influence of these men upon the development of gynecology, we must dwell for a moment on some of their contemporaries and take into account the state of medical science in that day. A retrospective glance carries us back to the art of surgery before the discovery of anesthesia, when the time consumed by an operation was of the utmost importance and the outstanding surgeon was the man who possessed the greatest amount of manual dexterity. Such a surgeon short-

ened the painful ordeal, and was in much demand whereas the man who "niggled" over an operation was avoided by the physician and the patient alike.

Possibly the most skillful surgeon of his time in England was Robert Liston, the friend and preceptor of Syme. An amputation of the thigh performed by this man, including the making of the flaps, the sawing of the bone, and the detachment of the limb, is recorded as having been accomplished in twenty-five seconds.

James Syme (1800-1870) was one of those who benefited by the discovery of anesthesia. So far as manual dexterity goes it was reported that he could not compare with his contemporaries, Liston and Ferguson, and that he left London and returned to Edinburgh where his deficiency would be less noticed. With the advent of anesthesia, Syme became an outstanding figure. Surgery no longer reached its height in mere rapidity of action; there was time for perfection in technic; new fields were opened for treatment, surgical pathology at last could be studied adequately, and the patient could be relieved of the horror of an operation.

Syme was appointed to the Chair of Clinical Surgery at Edinburgh in 1833. After visiting him in 1862, Marion Sims declared: "I have seen great surgeons operate all over the world, but I have never seen such an operator as Dr. Syme." Personally Syme was the embodiment of the old-fashioned gentleman. He dressed immaculately, and there never was any appearance of hurry in his manner.

In 1839, much against Syme's will, there was elected to the Chair of Obstetrics at Edinburgh by a majority of one vote a young man of humble origin, who was destined to figure prominently, James Y. Simpson (1811-1870).

Even as an undergraduate his brilliant mind and unusual energy had greatly impressed his teachers. His inaugural address delivered at the time when he received the doctors degree at the age of twenty-one attracted the attention of John Thomason, Professor of Pathology, who appointed Simpson as his assistant. Thomason later advised Simpson to specialize in obstetrics which was then looked upon with more or less disdain, believing that his kindly manner would fit him for the care of women in childbirth.

His attractive personality and ability as a teacher made the class in obstetrics the largest at Edinburgh for the first time in its history.

Simpson is credited with making the earliest systematic study of the diseases of women. The addition of chloroform to anesthesia (1847), the invention of the obstetric forceps that bears his name, and the discovery of acupressure as a means of controlling hemorrhage (1859) are among his achievements.

As early as 1848 he saw the frightful results of overcrowding and uncleanliness among surgical patients in large hospitals and proposed

isolated smaller buildings that might be destroyed when they became a source of danger. His famous work on *Hospitalism* first appeared in 1867.

Simpson was a man of unusual appearance. Long tangled hair covered a head much above the average in size. His eyes, "sometimes piercing, sometimes almost feminine in tenderness," shone from under massive brows. His nose was coarse and had dilated nostrils. He had a strong jaw and a mouth "which seemed capable of being made at will the exponent of every passion and emotion." With his medium height, broad shoulders, short thick neck, and peculiarly rounded body and limbs, he was altogether a striking figure, and in any company commanding and impressive.

From the very beginning of his career he was the recipient of the highest honors; learned societies of every land paid tribute to his greatness.

He had much personal charm and there was no one in Great Britain who was more widely sought. "At his house," said Gross, "there was a constant round of hospitality." Interesting guests frequented his table and distinguished visitors came from a great distance. He was a ready and attractive conversationalist "brimful of accounts of great personages, ghosts, murders, and church affairs."

Up to this time ovariotomy in Great Britain as in other countries had made slow progress. Lizars in Edinburgh had performed the operation in 1825, and Clay of Manchester undertook it in 1842. The frightful mortality that followed its use aroused great opposition. Syme exerted his influence against it, and Simpson was unwilling to expose a patient to such a danger.

One of the most successful ovariotomists of his time was Isaac Baker Brown (1812-1873). He adopted methods which it is said "lowered the mortality to one-half." He dropped the pedicle, securing hemostasis by division with the cautery and ligatures cut short. Keith who succeeded Brown depended almost entirely on cauterization, performed slowly and with complete charring at the line of division.

Spencer Wells (1818-1897) an ovariotomist who acquired world-wide renown was seven years younger than Simpson and only twenty-eight when the discovery of anesthesia gave new impetus to surgical work. Although in 1854 he assisted Baker Brown with an ovariotomy he did not at that time approve of the operation believing that the risk of invading the peritoneal cavity was insuperable. During his experience in the Crimean War, he discovered the ability of the peritoneum to take care of itself. Two years after his return to England in 1856 he performed his first ovariotomy which proved a complete failure, but by 1880 he had done the operation one thousand times. His experience with this surgical procedure exceeded that of any of his competitors. In his

Bradshaw lecture in 1890 he reported 1,378 operations. Wells' ovariotomy clamp was finally discarded, and he contributed nothing to ovariotomy beyond such observations as accrued from the large number of operations he performed. Nevertheless he was its chief advocate and all the changes, the ebb and the flow of the development of the procedure centered about him.

The work of Brown, Keith and Wells must have influenced both Syme and Simpson in their views, for Syme in 1865 spoke of Wells' work and its promise for the future, and Simpson in one of his last lectures said that ovariotomy was a "fairly legitimate surgical operation."

There is little doubt but that the discovery of anesthesia hastened the development of pelvic surgery just as it enlarged the field in general. However, the prevalence of postoperative sepsis was frightful and interfered with a wide adoption of the operation as an established method of treatment. "Unhappily," says Allbutt, "this new enfranchisement of anesthesia seemed an ironical liberty of nature," who with the one hand gave and with the other took away what she had given.

The concept of the transmission of diseases was not new; it existed even from the remotest times as is shown in the writings of the ancients. But whatever had been said of the value of segregation and chlorinization was more or less disregarded by surgeons whose theories regarding wound infections remained extremely vague.

The surgical habits of the day provided the most excellent grounds for the propagation and transplantation of hospital diseases and "no shame was felt for the good old surgical stink that at all times pervaded hospital wards" (Godlee).

The prevailing state of mind relative to surgical cleanliness is shown by the following circumstance: When Isaac Baker Brown lost a patient in 1854, he said to Wells who had assisted him in the operation, "it's the peritonitis that beats us." Although he recognized the evil he could scarcely have grasped its significance for a year (1869) after his book on ovariotomy appeared, he brought out one on "Scarlatina" in which he carefully described his plan of making applications to the throat.

It is a remarkable fact that Brown lost 26 of his first 50 patients and only 4 of his last 50; this great improvement he attributed to the method of treating the pedicle. One cannot help but wonder whether without realizing its importance, he had adopted some other measure also that prevented the transmission of infection from his scarlet fever to his surgical patients. Whatever the true explanation may be, his success began in 1865, the year in which Lister inaugurated his principles of antisepsis, an innovation that changed the whole complexion of surgery.

The epoch-making work of Joseph Lister (1827-1912) must not be regarded as merely the practical application of the discoveries of an-

other; it was rather the culmination of many years of study and inquiry, as to the origin and the morphology of inflammation. He had long sought for an explanation of postoperative morbidity and mortality in the hope that in some way they might be lessened or prevented. With his thorough understanding of the most pressing question that had to do with surgery "he was watching from the heights" as Allbutt has expressed it and immediately saw in Pasteur's discoveries the answer to his problem.

The photographs of Joseph Lister show a broad high forehead, a finely chiseled nose of good proportions, a well-formed chin and a wide expressive mouth. His manner was dignified and this aroused in younger men and women who did not know him a certain amount of awe. To them he might appear solemn and devoid of a sense of humor; but his intimates knew that he appreciated wit as well as any one, although he was intolerant of irreverence or vulgarity.

His students, house surgeons, and assistants idolized him: there sprang up quickly an affectionate regard for the "chief" which they felt was returned.

To his patients he was interested and sympathetic in his attention: his gracious manners and his thoughtful mien gave one an impression of power and resource, a mastery of the situation and a preparedness for "those possible emergencies that haunt the minds of nervous patients."

About the time that Lister began the use of carbolic acid, another figure appeared that was destined to loom large on the surgical horizon. It was that of Lawson Tait (1845-1899) whom William Mayo styles "the father of abdominal surgery." Tait had been an assistant and close associate of Simpson's as early as 1862 and had served also with Syme. He was only twenty-three years old when he boldly essayed the then highly dangerous operation of ovariotomy.

Tait was reluctant to accept the principles advocated by Lister, and abandoned them after a brief half-hearted trial. He greatly admired Syme, the father-in-law of Lister, and from the very first adopted some of the habits of Syme in his surgical work, namely, those of neatness and cleanliness, not only in his person, but also in the conduct of his surgical wards.

Tait soon passed beyond the limitation of ovariotomy to ovarian tumors and was the first to perform the operation for other reasons, removing in February, 1872 the slightly enlarged ovary of a woman who had suffered with pain.

It was not long after (August, 1872) that Robert Battey of Georgia removed both ovaries from a woman with an infantile uterus who had no menstrual flow but suffered with recurring and painful molimina; Battey suggested the employment of his operation also for the purpose of

arresting menstrual hemorrhage in myoma uteri, and for the relief of certain nervous symptoms that defied all other methods of treatment.

Wisdom and moderation governed Battey's own use of what he termed "normal oophorectomy" as was evidenced at the International Gynecological Congress in London in August, 1881 when he stated that in his entire experience he had found only 16 cases in which he felt justified in performing this operation. In reviewing the discussion, the *Medical Times* and *Gazette* expressed surprise that Battey himself had had so small a number of cases, whereas Tait and Savage reported more than a hundred from Birmingham. The views of the debators were scarcely to be reconciled, but as was revealed later, Battey and Tait were discussing different procedures.

Tait was removing ovaries but what was more important, he was also removing diseased tubes. Up to this time inflammation outside the uterus was generally believed to have its seat in the cellular tissue, but Tait revealed the part it played in the pathology of the tubes, and performed salpingo-oophorectomy.

By 1888, Tait's views relative to the incidence and morbid anatomy of tubal disease as well as his aseptic surgery had received recognition on both sides of the Atlantic. Nevertheless there still existed some skepticism concerning the frequency of salpingitis, and some confusion between oophorectomy and salpingo-oophorectomy.

As indicating this state of affairs reference may be made to a letter of inquiry from J. Henry Carstens to the editor of the *American Journal of Obstetrics* in 1883 asking for information concerning the difference between Battey's operation and Tait's operation.

A noteworthy achievement and a milestone in the advance of gynecology was the immediate operation for ruptured tubal pregnancy, a procedure which Tait was the first to perform in 1883. A series of 35 cases with only two deaths speedily followed.

Physically, Tait was a short broad-chested and bulky man; like Simpson he had a large head and long hair, and between them there was great resemblance. His face was grave and plebeian. His hands were short and broad also like Simpson's, but whereas Simpson's fingers were said to taper, Tait's were quite the reverse. So far as appearances went it would have been difficult to imagine more unsuitable hands.

What he had to say he put in as few words as possible, and when he spoke his lips hardly moved. "He was a severe and formidable critic of loose thinkers and careless writers." He was opposed to the germ theory and to vivisection. His conclusions upon a subject were based upon his deductions made from a practical standpoint. He had no imagination, no scientific bent. Some men, said McKay, his biographer, have a love of truth so innate that in an argument the demonstration of the truth gives them greater satisfaction than the proof that their op-

ponents are wrong; but it was otherwise with Tait, for he gloried in the utter discomfiture of his opponents.

He was a bold and fearless surgeon but not rash. To his assistants he appeared equal to any occasion and created a feeling of confidence.

These men were giants sprung from British soil. We marvel at their industry and pay tribute to their achievements. As we reflect upon their lives so filled with moving events, we understand more clearly the difficulties they surmounted and the influence they exerted.

We need go no further. The successors of these men inspired by the examples set before them have carried on the torch of medical progress in Great Britain. They have contributed their full share to the warp and the woof of gynecology, woven by workmen from all quarters of the world. We know and gratefully acknowledge their accomplishments.

James Harvey Robinson in his book *The Ordeal of Civilization* says that in history the important point is a "realization of how things came about."

"This realization opens our eyes wider upon matters as they now stand and at the same time suggests more ingenious ways of forwarding their improvement."

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# A STUDY OF A NEW AND POTENT ERGOT DERIVATIVE, ERGOTOCIN

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## INTRODUCTION

THE writers have reported already their adaptation of a method of study of uterine motility previously utilized by others, including Bourne and Burn, Moir and Rucker. This method was used in observations of the action of various drugs supposed to affect uterine contractility. The effect of some of these therapeutic agents was presented before the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons in September, 1933. Among these observations were some upon ergot. They were made mostly upon the uterus in the immediate postpartum period.

Our interest in this work was to evaluate the utility of ergot preparations and of the pure ergot alkaloid in obstetrics. It is well known that many of the ordinary fluid extracts prepared by many pharmacopeial methods are unreliable in their effects. This has been a debatable issue for many years. It was assumed that ergot preparations contained some

principle which in time underwent deterioration. Innumerable attempts had been made to stabilize these preparations. All of the methods had as their objective the preparation of an extract uniform in effectiveness when assayed by either the pharmacopeial or the Broom-Clark methods. Some means of stabilization of ergot included the addition of reducing agents, the control of hydrogen ion concentration, exclusion of oxygen, etc. If one bears in mind what we know now of the active principle of ergot, namely ergotocin, it is obvious that the real difficulty was not always with the ergot preparations but with the various standard methods of testing ergot potency. In 1932, Moir suggested that the aqueous B.P. extract of ergot contained a substance which when given by mouth produced a prompt oxytocic action. He claimed that the activity of the aqueous B.P. extracts could not be due to the known alkaloids, for the concentration of these alkaloids in this preparation was too low. He further claimed that the aqueous B.P. extract was a reliable drug. In the light of our present study, this statement of Moir is not entirely correct, in that the potency of a preparation of ergot is dependent on the amount of ergotocin contained in the crude drug as well as upon the method of extraction.

Early in 1932, Prof. M. S. Kharasch and Dr. R. R. Legault undertook a study of the chemistry of ergot under a grant from the Research Corporation. It was natural that they should become interested in the principle responsible for the oxytocic activity of ergot and a cooperative study of the problem was undertaken by the two departments. The first step in our investigation was to separate the defatted ergot into two fractions, one containing the known alkaloids ergotamine, ergotoxine, sensibamine, ergoclavine, and most of the débris, the other fraction containing the unknown oxytocic substance or substances. This was evident from the fact that the first fraction showed little and variable activity; the second fraction which we designated as nonalkaloidal to distinguish it from the portion containing the known alkaloids included ingredients which gave uniformly typical ergot responses. Thus, early in our investigation it was evident that the typical oral oxytocic effect of ergot did not reside in the known alkaloids, a fact later corroborated by a study with the pure alkaloids. We have fractionated this "nonalkaloidal" fraction and tested the activity of the different materials. The potency of these fractions was always carefully checked by their administration to the puerperal woman. A careful kymographic record of its action was made in each case. Thus, chemical progress was always controlled by pharmacologic assay on the human subject. After many months we finally arrived at an ingenious technic for rapidly obtaining a new active principle in almost pure form, suitable for therapeutic administration from this crude nonalkaloidal fraction.

These studies of ergot and its various components were reported in November, 1934, at the meeting of the Central Association of Obstetricians and Gynecologists. We described the new active principle isolated from ergot and some of its chemical, pharmacologic, and clinical properties. It was found to be very active in doses of 1.2 to 3 mg. when administered orally. It was unlike the known alkaloids of ergot, chemically and pharmacologically. It was, undoubtedly, responsible for the major oxytocic activity exhibited by the drug.

Early in December of 1934 we finally isolated this new active principle in crystalline form. These crystals were found to be therapeutically active in doses of less than 0.1 mg. when given intravenously. We have agreed to call the new substance "ergotocin." Since that time we have continued our studies of this interesting new active principle and corroborated all the results previously reported. We have likewise

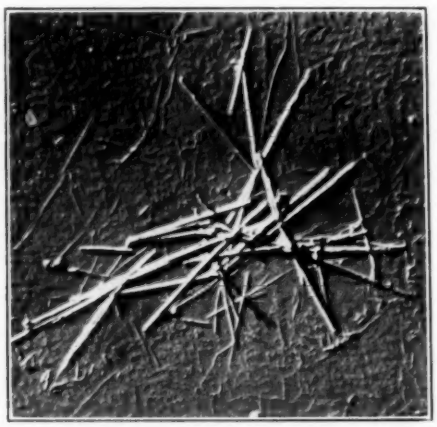

Fig. 1.—Photograph of crystals of ergotocin maleate.

progressed with a thorough chemical, pharmacologic and clinical study of ergotocin. Dudley and Moir, in March, 1935, reported the isolation of an active oxytocic principle from ergot.

## CHEMISTRY

The empirical formula of ergotocin is $C_{21}H_{27}N_3O_3$. It is a colorless, crystalline material, appreciably soluble in water, imparting to the latter a weak alkaline reaction. It may be crystallized in long, fine needle-shaped forms from such solvents as chloroform, benzene, and trichloroethylene, but not from hydrophyllic solvents such as alcohols or ketones (Fig. 1). When ergotocin is heated in a melting point tube, it begins to darken at 155° C. and melts sharply with decomposition at 159 to 160° C.

Ergotocin is very soluble in the lower membered aliphatic alcohols. It is only slightly soluble in nonpolar solvents, such as benzene, ethers, etc. It is very soluble in dilute aqueous solutions or organic or mineral acids. Solutions in dilute polybasic aliphatic organic acids are stable at ordinary temperatures and

may be sterilized at the boiling temperature of water without an appreciable loss of oxytocic activity and without imparting color to the solution.

In contrast to the behavior of the known ergot alkaloids, ergotocin in the form of the free base or as a salt is not precipitated from solution by the addition of Mayer's reagent in a dilution exceeding one part in six thousand whereas, under the same conditions, the ordinary ergot alkaloids are precipitated in a dilution of one part in a million or more.

Ergotocin gives a blue color, in acid solution, with paradimethyl aminobenzaldehyde. It also gives a blue color with Folin-Denis' phenol reagent.

The ultraviolet absorption spectrum of ergotocin is very similar to that of the known ergot alkaloids. The difference is one of degree rather than of kind. There is a minimum at 2700 A° and a maximum at 3100 A°. It is interesting to note that it has a very high coefficient of absorption of light in the region of the ultraviolet. However, in the region bordering the visible, practically no light is absorbed.

In contrast to the known ergot alkaloids, ergotocin does not give off a molecule of ammonia when treated with alkali. However, under alkaline hydrolysis a product is liberated which appears from all properties so far examined to be identical with lysergic acid.

Ergotocin forms well-defined crystalline salts with certain polybasic acids. These acids include the aliphatic polybasic acids and phosphoric acids. The monobasic and other mineral acids do not form crystalline salts with ergotocin. The salts of the polybasic acids have no characteristic melting points; they decompose within a short temperature range.

As would be expected, ergotocin is optically active. It is levorotatory and its salts are dextrorotatory. The specific rotation of the maleate in water is approximately +77°.

The question whether ergotocin is an alkaloid or a nonalkaloid is a trifling one. In our previous contribution we stated clearly the criterion we used for describing what we termed the nonalkaloidal portion of ergot, from which ergotocin was finally obtained, and also what we termed the alkaloidal fraction which contained the so-called "known ergot alkaloids."

We wish to clarify our position and statements and are incorporating a short analysis of the status of the chemical opinions regarding alkaloids.

The term "alkaloid" was recommended at a time when very little of the chemistry of naturally occurring substances was known, and it was based mostly on a limited knowledge of the field and a limited vision on the part of the originator of the word. A quotation from Henry's book, *The Plant Alkaloids,* is most pertinent. It indicates how loosely the term could be used and how difficult and unreliable, and therefore uncertain in its meaning, it is to term naturally occurring nitrogenous substances alkaloids, or nonalkaloids.

The word alkaloid was at first used to describe all organic bases, including the natural alkali-like substances which occur in plants. At the time this name was introduced comparatively few of these latter substances were known, and these were all alike in possessing basic properties and in exhibiting physiologic activity. These two characteristics, in conjunction with their complex structure, have made it possible until recently to regard the natural alkaloids as forming a well-differentiated group of chemical compounds, but recent work has tended to render indistinct the border lines between this and other groups. On the one

hand, such simple basic substances as ammonia and methylamine, and on the other, substances that contain nitrogen and are yet acidic rather than basic have been found in plants. And, again, complex substances closely related to typical alkaloids and which must be regarded as belonging to the class of alkaloids, though they have no marked physiologic action, are known. König proposed to avoid this difficulty by confining the name alkaloid to naturally occurring pyridine derivatives, but this rules out such important substances as the purine and glyoxaline derivatives, and for that reason can hardly be accepted as a satisfactory use of the name.

One must bear in mind that since this work of Henry has appeared, a number of simple nitrogenous substances, such as amino acids, have been isolated from plants, for instance, asparagine, etc. Are these substances to be classed as alkaloids? Other authors define the term alkaloids as "basic substances occurring in plants which contain in their constitutions pyridine, quinoline, isoquinoline or pyrrol or pyrrolidine ring, or several rings." If this is used as a basis of classification, it is obviously impossible to state whether a substance is an alkaloid or not, until the complete chemistry of the substance is known. The present authors have always deplored the indefiniteness of the term alkaloid and prefer to speak of the chemical substances by their chemical characteristics rather than by their source or origin, or loose empirical classification. However, in our laboratory, and in some of the papers we have published, we have found it convenient to restrict the term "alkaloids of ergot" to substances which will give a precipitate with Mayer's reagent in a very high dilution, such as 1:200,000 or 1:1,000,000, and not necessarily to all nitrogenous substances that occur in ergot. For otherwise, on the basis of some definitions, we would have to apply the term alkaloid to the following nitrogenous substances which have been isolated from ergot: leucine, isoleucine, valine, tyrosine, histidine, trimethylamine, putrescine, cadaverine, isoamylamine, tyramine, histamine agmatine, choline, acetylcholine, betaine, ergothioneine, uracil, guanosine, vernine, secale, amino-sulphonic acid. We believe that such a classification as we have adopted is perfectly valid in the restricted sense used by us. If the criterion we have outlined, namely, precipitation with Mayer's reagent, is used, then we have a perfect right to speak of alkaloidal and nonalkaloidal fractions in that sense, or certainly until the structure of the materials is definitely established.

With the isolation of the active component responsible for the oral effectiveness of ergot, and the establishment of its empirical formula, $C_{21}H_{27}N_3O_3$, the entire question whether the active principle is an alkaloid or nonalkaloid loses its argumentative appeal except for nonchemists. We have shown definitely that ergotocin is not precipitated by Mayer's reagent in a dilution higher than 1:6,000, while ergotoxine, ergotamine, and sensibamine are precipitated by that reagent in dilutions as high as 1:2,000,000. This is a unique characteristic which,

according to our definition and that used also by many other chemists, would differentiate alkaloidal from nonalkaloidal materials. We reiterate that the entire term alkaloid has outlived its usefulness and carried no meaning whatsoever, and it is high time that the term either be rigidly defined or be given up altogether.

In all of our future communications we shall dispense completely with that term and speak of ergotocin as a definite chemical compound rather than as an alkaloid or nonalkaloid. This decision is based upon our belief that the term alkaloid has lost completely its original meaning. It is loosely used and does not carry a definite concept, except as "a substance contains nitrogen," and the whole argument is much ado about nothing. We prefer not to use a word for the classification of chemical substances that cannot be rigidly and uniquely defined.

## PHARMACOLOGY

*Experimental.*—The pharmacologic studies on animals have been carried out largely by Chen and Swanson. This has been published elsewhere. The general conclusions from work done in experimental pharmacology are: that this principle, ergotocin, has a powerful oxytocic action on both isolated and puerperal mammalian uteri; that the methods of the assay of ergot need revision. The U.S.P. cockscomb method is not specific. Cocks developed gangrene of the comb when injected daily with 1 mg. of ergotocin. It is more potent gram for gram than ergotoxine. The reactions obtained in the cockscomb by ergotocin, ergotoxine, and fluid extract of ergot, are indistinguishable. Unlike ergotamine or ergotoxine there is little inhibitory action on epinephrine by ergotocin, hence the Broom-Clark method is not applicable.

The isolated uterine response may be used as a method of assay inasmuch as the uteri both of virgin guinea pigs and of rabbits react to ergotocin. The former appears to be more sensitive but the latter seems to be more reliable. The postpartum uteri of dogs respond to tests made following the introduction of a hydrostatic bag.

Its toxic action is minimal. In the form of a maleate, ergotocin was found to have a minimal lethal dose of 250 mg. per kg. in mice and of 80 mg. in guinea pigs. When injected intravenously tetanic convulsions preceded death in these animals. No toxic symptoms were manifested in two dogs which were given 1 mg. per day for twenty days, though one had an evanescent albuminuria. The effect on involuntary muscles was shown by the production of mydriasis in a rabbit's eye, by constriction of a frog's limb vessels, and the relaxation of isolated rabbit's small intestines which latter effect can be abolished by the previous application of ergotamine. This behavior may indicate some stimulating action on the sympathetic endings. Ergotocin sometimes causes a pressor action

in pithed cats but produces a depressor action in anesthetized animals. Large doses suppress respiration. The metabolic rate is increased in white rats by intravenous injections of this agent.

*Human.*—Most of our studies are based upon observation of the sixth- to eighth-day postpartum uterus by the method previously described. We have used varying doses administered by each of the following methods: oral, sublingual, intramuscular and intravenous. The graphs illustrating the kymographic tracings of uterine contractility following the oral, sublingual, and intramuscular administration of ergotocin are similar and comparable. It is outstanding that the tracings derived from uterine contractions following its intravenous administration are markedly different, are typical and unlike any tracing we have obtained from any other oxytocic agent.

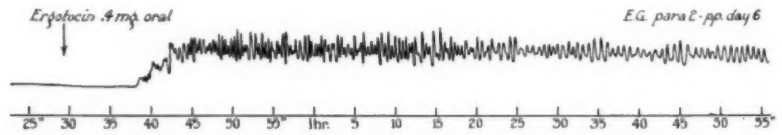


Fig. 2.—Graph obtained ten minutes after the oral administration of 0.4 mg. ergotocin. The stepladder-like rise of the curve shows the development of tetany. The contractions recurred every fifteen or twenty seconds, gradually becoming further apart at the end of the first hour. Uterine motility still persisted at the end of two hours.

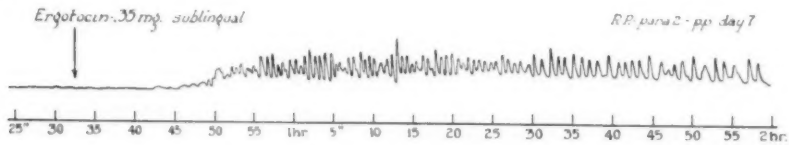


Fig. 3.—Graph obtained following the sublingual administration of 0.35 mg. of ergotocin.

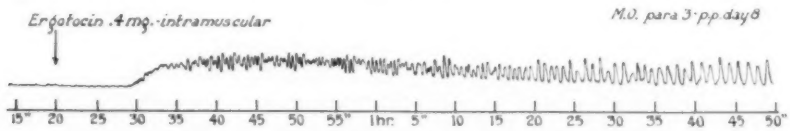


Fig. 4.—Graph obtained after the intramuscular administration of 0.4 mg. ergotocin. Note that the induction period is almost as long as by the oral route.

The tracings following the oral, sublingual and intramuscular administration of ergotocin are so similar that one description will suffice for all (Figs. 2, 3, and 4). The individual variations in these tracings may be accounted for by the variability in the reactions of the uterus of individual patients. The effect of the administration by these methods is not shown on the tracings for about eight to twelve minutes following its administration. The first noticeable effect is in the onset of slight contractions with a gradual increase of tonicity. This increased tone is clearly shown by the gradual ascent of the curve. The excursions of the needle show a gradual increase in the amplitude of the waves, indicating more marked uterine contractions. Not all of these contractions are of uniform strength, but they seem to run more or less rhythmically in groups of weaker and stronger contractions. At first the time interval between these contractions is longer, but this gradually becomes shorter. These frequent waves of contraction are maintained at a fairly constant tonicity level after the maximum tone is once attained. After a lapse of about forty minutes the contrac-

tions become less frequent, but the amplitude remains about the same with the corresponding tonicity level. The tracing shows a diminution in both the amplitude of the contractions and the uterine tone after about an hour and a half, though there is evidence of continued uterine motility for three or more hours after the initial administration of ergotocin.

In striking contrast to the graphic tracings just described are those following the intravenous administration of ergotocin (Fig. 5, *A*, *B*, *C*). Here again there is slight variation in the tracings derived from individual patients, but in all of the tracings there are striking and typical characteristics. The relatively inactive uterus shows sudden activity almost instantaneously after the administration of intravenous ergotocin. This is demonstrated by the almost vertical

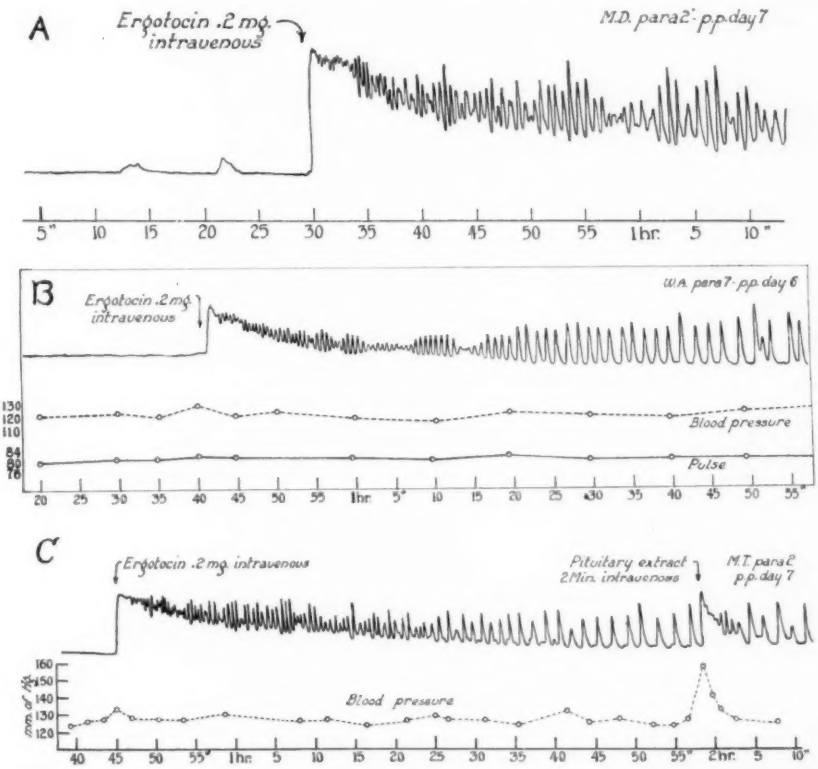


Fig. 5.—*A*, *B*, *C*, Graphs obtained following the intravenous administration of 0.2 mg. ergotocin. The almost instantaneous response of the drug is demonstrated by the abrupt rise of the curve fifteen or twenty seconds following the administration of the drug. Note the marked tetany which persisted for several minutes, after which tiny contractions began. These increased as the uterus gradually relaxed. Good tetany and motility were maintained for several hours.

ascent of the needle. This ascent occupies not more than fifteen seconds, at which time the tracing indicates that the uterus has reached its maximum tetany. Following this tetanic contraction the uterus begins to show slight intermittent contractions, the maximum point of which remains more or less at the maximum point of tonicity. The lower point of the contraction wave is below the level of the maximum tonicity but much above the level of the uterine tone prior to the administration of ergotocin. The tetany of the uterus gradually diminishes. The contractions imposed upon the tetanic state are at first of very low amplitude but gradually show more marked contractions and relaxations. The re-

maining portion of the tracings shows characteristics similar to those already described for the other methods of administration. The duration of the effect of this oxytocic agent continues for about the same length of time by all methods of administration.

We have previously called attention to some of the uterine reactions following the administration of large doses of ergotoxine ethane-sulphonate, ergotamine tartrate and sensibamine. We have given these drugs in doses of 3 mg. and more orally. The uterus remained relatively inert, following the administration of these alkaloids, for three-quarters of an hour and over (Figs. 6 and 7). In order to test the efficacy of ergotocin as compared with these agents in the same patients, we later administered ergotocin in approximately 0.4 mg. doses, both orally and sublingually, and have been able to secure the typical tracings previously described for this active principle. The administration of these alkaloids in large doses (2 or 3 mg.) by subcutaneous and intramuscular methods, while in some instances provoking uterine responses, did not excite uterine contractions to anything like the degree which was obtained by the use of ergotocin in much smaller doses. Furthermore, unpleasant reactions on the part of the patient, such as nausea, vomiting, and associated symptoms, occur from the former.

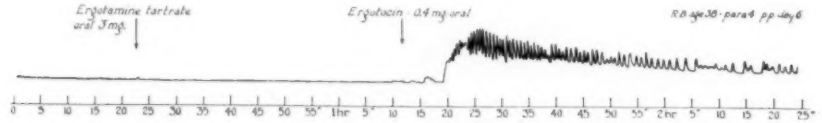


Fig. 6.—Ergotamine tartrate, 3 mg. orally, produced no contractions at the end of fifty minutes. About five minutes after the oral administration of 0.4 mg. of ergotocin a typical "ergotocin response" developed.

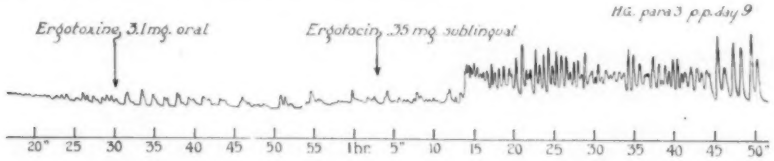


Fig. 7.—Ergotoxine, 3.1 mg. orally, produced no contractions at the end of one hour. About five minutes after the sublingual administration of 0.35 mg. of ergotocin a typical "ergotocin response" was obtained.

The difference in the uterine motility brought about by the administration of pituitary extract has been previously stressed. While the effect is perhaps equally prompt, the duration of increased uterine tone and contractility is very much shorter following the administration of pituitary extract than it is following the use of ergotocin.

The dosage of ergotocin is minimal. Effects are obtained by less than 0.05 mg., but the best response is obtained by the intravenous administration of approximately 0.2 mg. About twice this amount is used for other methods of administration. In a few cases slight nausea, with or without vomiting, is incurred, but such reaction is unusual. Much larger doses have been given without unpleasant manifestations. While the margin of safety is very wide, we feel that the minimum uniformly effective dose should be used.

## THERAPEUTIC EFFECTS

Inasmuch as the unfavorable effects of the administration of some other oxytocics, such as pituitary extracts, upon blood pressure and urinary output are known, we have felt it necessary to observe some of

these reactions upon the patients who have received ergotocin. We have observed these results in a considerable number of cases, some of whom were apparently normal and others of whom presented definite evidence of disturbed vascular balance with marked hypertension. In a group

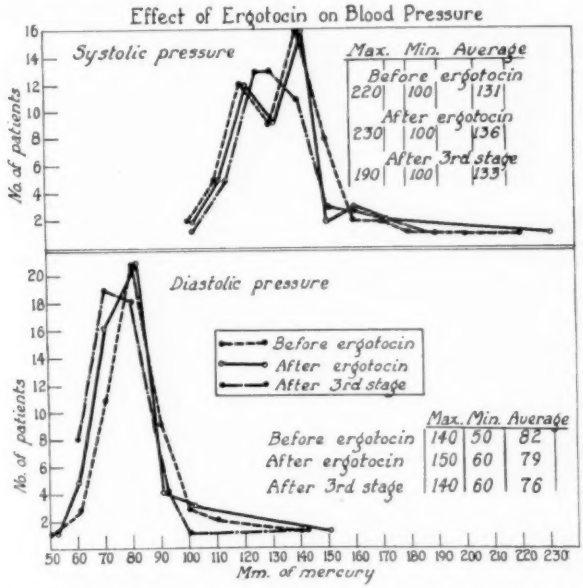


Fig. 8.—Graph showing the effect of ergotocin on the blood pressure.

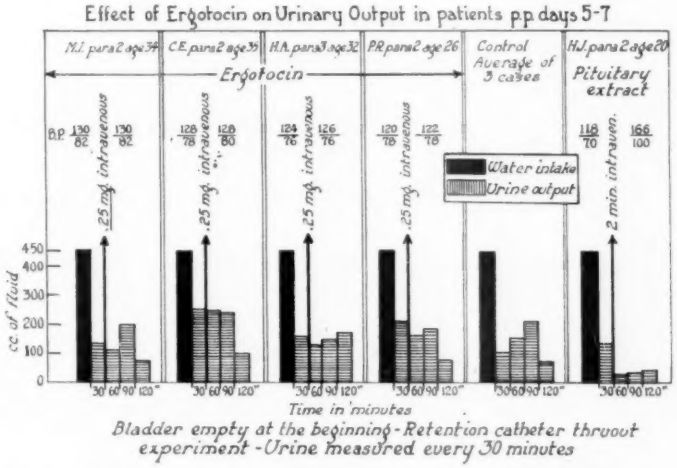


Fig. 9.—Graph showing the effect of ergotocin on the urinary output.

with no evidence of cardiovascular renal diseases, we found the average blood pressure before the administration of ergotocin was 129/80. The maximum blood pressure was 142/100 and the minimum was 100/50. The corresponding readings following the administration of ergotocin were 129/79 as an average, 148/100 for the maximum, and 100/56 for

the minimum. In the other group, with abnormal blood pressures, the average reading was 162/92, the maximum was 220/150, and the minimum was 144/70, before the administration of ergotocin. There was little change following the use of this drug as the average, maximum, and minimum are seen to be at approximately the same level (Fig. 8). We feel justified in concluding that both the patients with normal and those with abnormal blood pressure show little or no alteration as a result of the administration of ergotocin. This is a very important fact inasmuch as most oxytocics, notably pituitary extract, have a tendency to produce marked rise in blood pressure which action has inherent dangers, especially in patients with a disturbed vascular balance.

We also observed the effect of this drug on urinary output. Twelve cases were tested during the postpartum period. The bladder was emptied by means of a retention catheter. The patient was then given

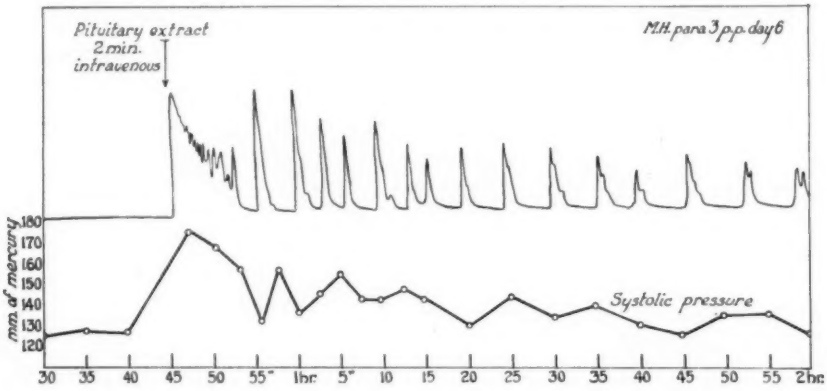


Fig. 10.

450 c.c. of water by mouth. The urinary output was measured thirty minutes later when 0.5 mg. of ergotocin were given intravenously, following which the blood pressure, pulse and pupillary reactions were observed. There were no alterations in blood pressure or pulse. Occasionally a slight dilatation of the pupil was noted. This was very slight and transient. The urinary output was measured every thirty minutes during a period of two hours. Control patients were observed in the same manner, without the administration of ergotocin. The output in these groups was comparable. A similar experiment was done on a number of women using 2 minims of pituitary extract intravenously. The urinary output was markedly suppressed. The graphs of these experiments show the results quite clearly.

As a result of these observations, we reached the tentative conclusion that the administration of ergotocin in therapeutic doses has little or no effect on the blood pressure curve of patients with or without hyperten-

sion. We also believe that there is no effect on urinary output. Both of these facts are of considerable importance, particularly in dealing with patients manifesting evidence of the various types of toxemia.

We have also noted the possibilities of alterations in pulse rate and respiration in all our patients. There has been practically no change in either the pulse or the respiration rate.

## CLINICAL OBSERVATIONS

It is, of course, too early to reach any final conclusions relative to all the clinical applications of this recently isolated principle of ergot. We have, however, had some opportunity to observe the effect of ergotocin on various puerperal states. The bulk of our observations pertain to its use during the postpartum period and the third stage of labor. We have had a considerable opportunity to observe its effect upon the uterus exposed through an abdominal incision during the progress of hysterotomy and cesarean section.

We have observed the results obtained in other smaller groups of cases. The beneficent effect of its use in the treatment of abortion, especially incomplete abortions with bleeding, is apparent from a few cases in which we have used it. The administration of 0.25 mg. at four-hour intervals was followed by uterine contractions and the expulsion of retained secundines and a control of the hemorrhage. Most of these patients had no subsequent hemorrhage and required no operative procedure. There are a few interesting observations relative to its use in these cases of abortion. In one patient who gave a history of idiosyncrasy to ergot, there was nausea and vomiting on two occasions following the use of ergotocin. This patient also vomited after the administration of stypticine intramuscularly. In some cases of therapeutic abortion the emptying of the uterus was accompanied by the administration of ergotocin. The uterus could be felt to contract firmly. In one case, in which spinal anesthesia was used, the uterus contracted equally well. This confirms the experimental observations indicating that ergotocin may act through the sympathetic system or directly upon the uterine muscle.

This drug has not been used during the first and second stages of labor. We feel that the same or even greater dangers attend the use of ergotocin during these stages of labor than would accompany the administration of any potent oxytocic drug. We have observed its action during the placental stage of labor in seventy-five cases. These cases are divided into two groups.

First, where the baby was delivered through the normal passages, 0.25 mg. of ergotocin was given intravenously in fifty-one of these cases as the second stage was being completed. The uterine muscle contracted firmly and promptly after

this administration. The placenta separated spontaneously in all of these cases with one exception. Delivery of the placenta was spontaneous after an average duration of a little over four minutes. The maximum time was fourteen minutes and the minimum time was two minutes. In the one exceptional case the patient gave a history of having had a retained placenta followed by manual removal the year previously. In this patient it was necessary to remove the placenta manually one hour and eighteen minutes after the completion of the second stage. The blood loss in these cases was minimal, the average being 100 c.c. with a minimum of 10 c.c. and a maximum of 300 c.c. In all of these cases the uterine response was good with firm contractions and no subsequent bleeding.

In the second group of cases the behavior of the uterus during the third stage of labor was observed at cesarean section. We have, in all, twenty-four of these cases, in which 0.25 mg. of ergotocin was given intravenously as the baby was being delivered through the uterine incision. In all of these cases the uterine muscle contracted firmly, the uterine wall became blanched, its contractions drew the peritoneum into small folds spread over the surface of the uterus. These changes show clearly the marked tetany and contractility of the uterus. The placenta was detached smoothly from the uterine site and was gradually pushed into the incision with partial extrusion which could easily be completed by traction on the cord or by lifting it out manually. This separation was completed in an average time of about two minutes with a minimum lapse of one minute and a maximum of five minutes. Manual separation of the placenta from the uterine wall was unnecessary in any of these cases. The uterine cavity remained dry and the blood loss was minimal during the placental stage. The visualization of the uterus in these cases following intravenous use of ergotocin confirmed nicely our kymographic observations and demonstrated clearly its prompt and powerful effect upon uterine tone and contractility.

We define a postpartum hemorrhage as a condition where 500 c.c. or more of blood loss occurs in a postpartum patient. During this period of study we have had occasion to use ergotocin in seven such patients by the administration of 0.25 mg. intravenously. In all of these cases the uterus has responded actively, the hemorrhage has ceased, there has been no further hemorrhage and the postpartum period has progressed normally. No uterine tamponade has been necessary in any of these cases. The prior administration of pituitary extract and usual management had proved ineffectual in five of these patients. The blood loss was of such an extent that it was necessary subsequently to transfuse three of these cases.

As previously indicated, most of our studies and observations have been upon postpartum patients. We have already described the typical graphs which have been obtained and illustrate the observations made upon over a hundred cases. There have been other patients presenting evidence of subinvolution and uterine infection upon whom the clinical effect of the use of ergotocin has been noted. No kymographic studies have been made upon these patients. There are approximately fifty in this group. There are about fifteen patients who gave evidence of uterine

infection between the fourth and eighth postpartum day. Some of these patients received 0.4 mg. of ergotocin orally for three days, three times a day. Others of them received 0.2 mg. intravenously three times a day. Following the administration there was a primary increase in the lochia, contractions of the uterus were stimulated, the foul odor gradually diminished, the amount of lochia decreased, and the corpus progressively diminished in size. The general status of these patients was improved both subjectively and objectively. The uterus seemed to be well involuted at the time of discharge, which occurred about the tenth day in all of these cases.

The group of cases with subinvolution of the uterus, without evidence of infection, consisted of approximately thirty-five patients. In all of these instances the process of involution seemed to be favored by the use of ergotocin.

We have considered the possibility of using this very potent oxytocic for the purpose of inducing labor. We have been fearful of the dangers which might be incurred because of the powerful contractions and the marked tetany of the uterus which have been noted during the third stage and postpartum period. We have tried it in minimal doses in a few cases without very conclusive results. Somewhat larger and longer continued doses were used in one case where there had already been an intrauterine fetal death prior to its administration. In this case we seemed to secure some results from the attempt at medicinal induction. We are very hesitant about advocating the use of ergotocin for the induction of labor.

## CONCLUSIONS

We have isolated in crystalline form the active principle of ergot which is responsible for most, if not all, of the desirable oxytocic effect of ergot. We have designated this substance as ergotocin. It is potent in minimal doses by various methods of administration. It does not deteriorate readily and is constant in its action. It is relatively free from untoward or undesirable effects. Its margin of safety is very great as the degree of toxicity is very low. It has no apparent detrimental effect upon respiration, pulse, blood pressure, or urinary output. This emphasizes the value of its use in cases having evidence of cardiovascular renal diseases or toxemias where oxytocic action is required. We are not advocating its use during the third stage of labor, but believe it may be used during this stage as safely and more effectively than any other known oxytocic drug. It is extremely valuable in stimulating uterine contractions in the immediate and remote postabortal and postpartum periods. Its prompt effect in producing tetany and contraction of the uterus, and its prolonged action, make it of special value in the manage-

ment of postpartum hemorrhage. With the isolation of ergotocin the age-old problem concerning the oxytocic principle in ergot apparently has been brought to a close. We now have all the desirable, potent, oxytocic activity in ergot isolated in a crystalline material, stable, and nontoxic. Ergotocin can be used safely whenever oxytocic therapy is indicated.

REFERENCES

(1) *Davis, Adair, Rogers, Kharasch, and Legault:* Am. J. Obst. & Gynec. **29:** 155, 1935. (2) *Davis, Adair, Chen, and Swanson:* J. Pharmacol. & Exper. Therap. **54:** 398, 1935. (3) *Moir:* Brit. M. J. **1:** 1119, 1932. (4) *Adair and Davis:* Am. J. Obst. & Gynec. **27:** 385, 1934. (5) *Kharasch and Legault:* Science **81:** 388, 1935. (6) *Kharasch and Legault:* J. Am. Chem. Soc., June, 1935. (7) *Dudley and Moir:* Brit. M. J. **1:** 520, 1935. (8) *Koff:* Surg. Gynec. Obst. **60:** 190, 1935. (9) *Broom and Clark:* J. Pharmacol. & Exper. Therap. **22:** 59, 1923. (10) *Henry, Thomas Anderson:* The Plant Alkaloids, Philadelphia, 1913, P. Blakiston's Son & Co.

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## THECA CELL TUMORS

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A UNIVERSALLY accepted classification of ovarian tumors has not been presented as yet. The recent advances in our knowledge of these neoplasms has been based on our better understanding of the embryologic development of the ovary and on our realization that the gonadal hormones and their clinical manifestations may prove important factors in identifying tumor types.

In the early embryo the epithelial covering of the gonadal anlage becomes many layered and invades the underlying mesenchyme in the form of cords (Fig. 1). The cells in these cords later form the true parenchyma of the gonad. This so-called indifferent stage rapidly evolves into the definitive gonad, and the fate of the original invading cords vary with the type of gonad (male or female) that develops. In the male these cords form the tubular system of the testicle and possibly the interstitial cells. In the female these cell cords give rise to the forerunners of the granulosa cells and the theca interna cells.

Fischel and recently Schiller have suggested that these parenchymal cells of the ovary are the results of a transformation in situ of the mesenchymal tissue and though they have the properties of epithelial cells they are not really derived from the gonadal surface epithelium. Irrespective of which origin is accepted, the fact remains that in the ovary two cell types exist in the ovarian parenchyma, granulosa cell forerunners and theca cell forerunners destined to ripen in the later development of the gonad into mature granulosa and theca cells.

The parenchymal cells, both granulosa and theca interna, have definite common characteristics. They both store or form lipoid, and they both store or produce an estrogenic hormone. Zondek showed that the theca interna cells contain an estrogenic hormone in greater amount than in the granulosa. The lipoid also differs in the two types of cells; in the granulosa it is scant in amount, being found in quantity only when the cells are undergoing degeneration, while in the theca cells it is much greater in quantity in the normal functioning cell. In addition, in the granulosa layer it is mainly phospholipid whereas in the theca it is mainly cholesterol or the esters.

Both types of cells have an influence on connective tissue growth, apparently stimulating it to develop. This connective tissue has a tendency to hyalinize. This stimulating effect on the connective tissue

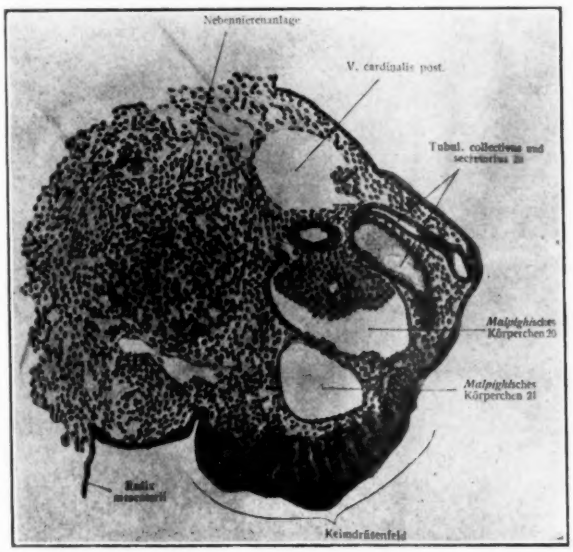


Fig. 1.—Illustrating invasion or mutation of mesenchyme into epithelial cords.

also seems a more marked characteristic of the theca cells. It has also been suggested by Löffler and Priesel and others, that the theca cells even may produce fine connective tissue fibrils a property that Schiller has emphasized as substantiating the mesenchymal origin of these cells.

It is natural to suppose that these immature granulosa cells and theca cells may give rise to tumors. R. Meyer and others have described tumors, termed by V. Werdt granulosa cell tumors, which have been accepted as having their origin from these unripe granulosa cells of the parenchyma.

Löffler and Priesel in two publications have reported ten cases, and Melnick and Kanter have added two additional cases that because of very definite gross and histological characteristics, they believed arose from the theca cells of the ovarian parenchyma.

We have been able to assemble five tumors which we believe fall into this group. In the ten cases reported by Löffler and Priesel, two occurred before the menopause. One in a young woman of eighteen the other in a mature woman of thirty-seven. The two cases reported by Melnick and Kanter, both developed after the menopause and in our group of five cases one occurred in a young woman of twenty-one years of age.

The following are the cases studied with the available clinical data. In view of the fact that three of the five were old cases and the specimens found in our collection of tumors, the clinical data were scanty and chemical and hormonal studies could not be undertaken.

CASE 1.—(Courtesy of Dr. Neuhof) R. M. was a married woman, aged forty-eight years. Her previous history was negative. The menstrual history was normal,

Fig. 2.—Case 1, showing large striated tumor, grossly yellowish white, in close association with dermoid cyst. Woman forty-eight years of age, no bleeding.

and there were no evidences of endocrine disorder. The physical examination revealed a ballotable tumor, apparently attached to the right adnexa, the size of a child's head. At operation the tumor was removed leaving the grossly normal uterus and left adnexa. The patient made an uneventful convalescence.

The specimen was composed of two distinct masses (Fig. 2), one a nodular oval tumor, hard yellowish white and encapsulated. This measured 18 by 15 by 10 cm. The second portion was a typical dermoid closely applied to the solid tumor but apparently not a part of it.

The solid tumor on section presented a gross appearance corresponding to some of the specimens described by Löffler and Priesel, and Melnick and Kanter. It showed small light yellow areas separated by septa of white connective tissue more or less uniformly distributed over the entire surface. The yellow areas varied from 0.5 to 1.5 cm. in diameter. The connective tissue septa varying in width from very fine strands to thickened bundles 5 to 7 mm. wide.

Histologically the yellow areas were composed of masses of elongated oval cells with blunt ends, or of polygonal cells with a vesicular or at times a deep staining

nucleus surrounded by a faintly staining vacuolated protoplasm. In some of the cellular islands the cells appeared as masses of spindle cells, suggesting a spindle cell sarcoma (Fig. 3). Fat stains demonstrated that these cells contained lipoid masses of varying size (Fig. 4). The globules are found mainly in the cells but appear to some slight extent in the interstitial tissue. The globules are doubly refractile.

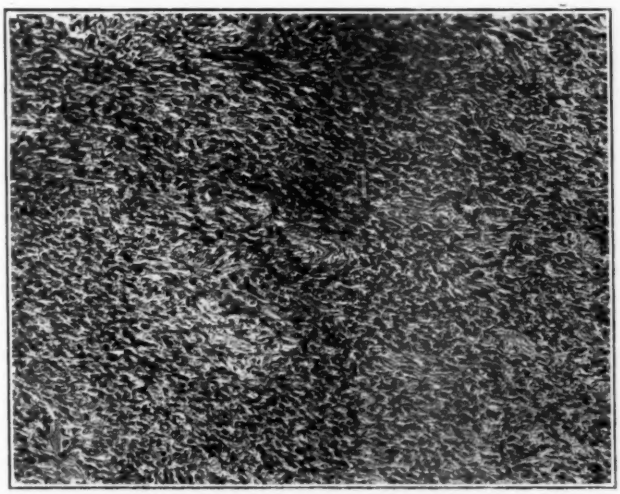

Fig. 3.—Masses of small, plump spindle cells suggesting sarcoma.

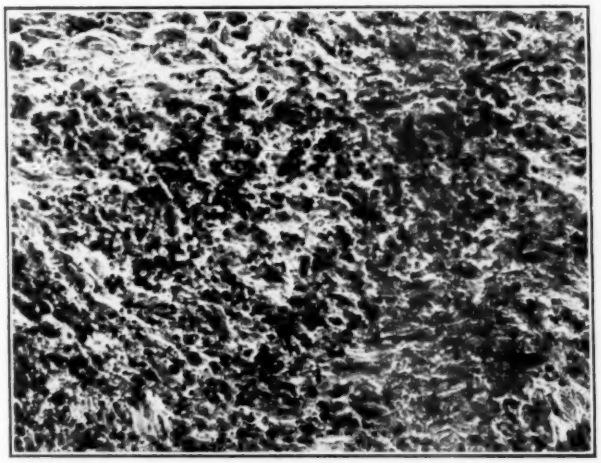

Fig. 4.—Graph obtained after the intramuscular administration of 0.4 mg. ergo-

In the cellular islands are found hyaline plaques (Fig. 5) of connective tissue surrounded by the spindle cells. Fine fibrils extend out from these hyaline plaques to separate the cells into small groups or even into isolated units. In some areas the connective tissue fibrils seem to enter or emerge from the spindle-like epithelioid cells.

The white septa are connective tissue bundles containing few cells. In the meshes of the bundles are found the remains of large polygonal epithelioid cells,

which cells also contain fat. The bundles are composed of fine fibrils possibly the products of the cells above described or the result of the stimulation by these cells of the intercellular substance. These fine fibrils may extend between the individual cells. There is a marked tendency for this tissue to undergo a hyaline change which can be especially well seen in the connective tissue islands already described.

The cellular areas were vascular, the vessels being both thin and thick walled and occasionally dilated. Pigment containing cells were found in the cellular areas (probably lipochrome) and occasionally in the vessel endothelium.

The tumor had been fixed before the nature of the growth had been determined so that hormone studies were not undertaken. However, a chemical estimation of the lipoids was made by Dr. Gerhard Rosenthal. The material was treated according to the method of Sabottka, Epstein and Lichtenstein. The tissue was finely chopped and extracted for several weeks with cold acetone. After the evaporation the residue was extracted with hot alcohol. It is presumed that in this fraction all the neutral fat as well as a certain proportion of the phospholipoids are contained. A second extraction of the chopped residue, left after the cold acetone and hot

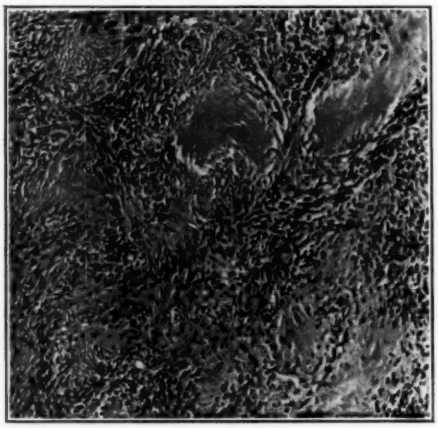

Fig. 5.—Hyaline plaques in cellular areas with fine connective tissue fibrils.

alcohol extraction, was made with hot acetone in the Soxhlet apparatus. This was extracted subsequently with ether and thus most of the lecithin (cephalin) and cerebrosides were obtained. Finally extraction with hot alcohol to obtain the remaining cerebrosides and sphyngomyelides was completed. Cholesterol and cholesterolesters were determined according to Bloor, phosphorus according to Kuttner and Cohen, and nitrogen by the micro Kjeldahl method (Table I).

The following is a résumé of the findings. The weight of the fresh material was 109 gm. The total lipoid extract was 2.99 gm. -2.7 per cent of the fresh material. All the weights in the table are in grams per cent of fresh material. The total phospholipoids of all three extracts amount to 0.352 gm. or 0.321 per cent of the fresh material.

The cholesterol and cholesterolesters to 1.180 gm. or 1.1 per cent. These figures show that we are dealing with a tissue of comparatively little lipid content, of which the cholesterol fraction is very high in relation to the other lipids, as well as to the fresh material. This is easily understood when one realizes that the bulk of the tumor is fat-free connective tissue. It has also been noted that the fat in

the cells is double refractile. Only about one-fifth is free cholesterol, the other part is esterified. The blood cholesterol and esters were studied and normal figures were obtained. Total cholesterol in the blood was 140 mg. Total cholesterolesters in the blood were 31 mg. In other words, the cells of the neoplasm either store or form cholesterol and cholesterolesters. The process is not due to a metabolic disturbance as evidenced by the normal blood figures.

TABLE I*

| GRAMS OF EXTRACT | TOTAL CHOLESTEROL | CHOLESTEROL OF THE ESTER | FREE CHOLESTEROL | CHOLESTEROL ESTER | PHOSPHORUS | PHOSPHOLIPIDS | BALANCE NEUTRAL FATS AND CEREBROSIDES |
|---|---|---|---|---|---|---|---|
| ACETONE EXTRACT (NEUTRAL FAT SOME LECITHIN) | 0.746= 684 mg. % | 0.630= 578 mg. % | 0.116= 106 mg. % | 1.06= 972 mg. % | 0.012= 11 mg. % | 0.312= 286 mg. % | 1.268= 1.1 mg. % |
| ETHER EXTRACT (MOST LECITHIN 0.01 SOME CEPHALIN) | 0 | 0 | 0 | 0 | 0.00056 =0.51 mg. % | 0.015= 14 mg. % | 0 |
| ALCOHOL EXTRACT 0.22 (CEREBROSIDES SPHYNGOMYELIDES) | 0 | 0 | 0 | 0 | 0.00096 =0.88 mg. % | 0.025= 23 mg. % | 0.195= 180 mg. % |

*All weight in grams-percentage of fresh material.

CASE 2.—G. H. was a patient on the Gynecological Service at Mount Sinai Hospital. She was twenty-one years old, had been married four years and never had been gravid. Her menses began at the age of eleven and up to her sixteenth year were regular and normal. From the sixteenth to the seventeenth year she had bled daily. Since her seventeenth year she had bled every other week, the periods lasting from five to six days. For four months she bled daily except for the past month during which time there had been no bleeding. She had also noted a definite enlargement of both breasts. The physical examination revealed the presence of a left-sided firm pelvic mass, the size of an orange, and a moderate hypertrophy of the breasts. At operation a left salpingo-oophorectomy was done removing a firm oval ovarian tumor with slightly irregular surface about the size of a tangerine (Fig. 6). On section it presented a yellowish color due to small islands of yellow tissue separated by connective tissue bundles resembling somewhat the tumor in Case 1. In addition small hemorrhages were present and several small cysts and one large one about 2 cm. in diameter were found.

The other ovary was normal, the uterus was soft, succulent but otherwise normal.

In the main the histologic findings resembled those described in Case 1. However, there was a tendency for the fibrous tissue to preponderate and the epithelioid cells were more vacuolated (Fig. 7).

Hormone studies were made of the tumor tissue by Dr. F. Spielman. The fluid from the cyst was examined but as only a small amount was available, conclusions cannot be definitely drawn. In amounts up to 0.5 c.c. the fluid did not contain one mouse unit of estrogenic hormone. However, in view of the fact that these cysts are degenerative in origin this finding is not unlooked for.

The tumor tissue itself when extracted showed the presence of one mouse unit per 0.75 gm. of tumor tissue, an amount greater than that found in the placenta. This finding seems to show that these tumors may either produce or store on estrogenic hormone and suggests that the cells of the tumor have some epithelial characteristics.

Since the operative removal of the tumor, the periods have returned to normal occurring every twenty-eight days. The patient now has had six normal four-day periods. Her breasts have grown smaller. This case is to be published in the *Journal of the American Medical Association.*

CASE 3.—(Courtesy of Dr. A. A. Berg.) H. C., a woman sixty-five years of age had an uneventful menopause fourteen years ago. For the past six years she noted an abdominal mass. For the past month she has noticed painless, odorless vaginal bleeding. The physical examination was negative except for the presence

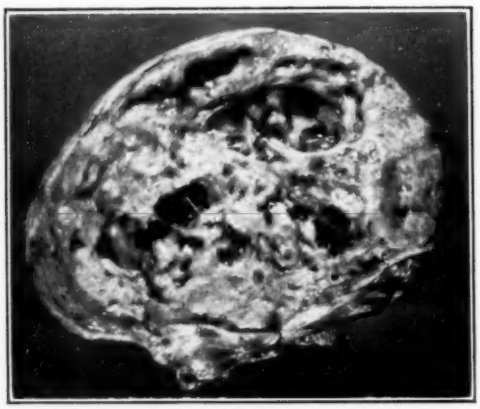

Fig. 6.—Case 2. Firm yellowish, white tumor with numerous degenerated cysts, twenty-one years old. Atypical bleeding, breasts enlarged, estrogenic hormone present.

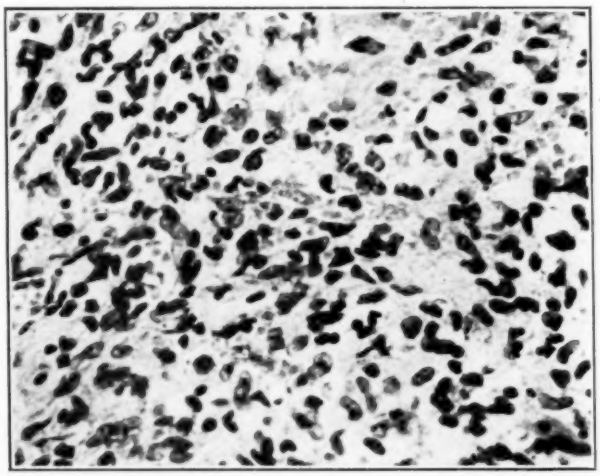

Fig. 7.—Cellular areas with connective tissue, vacuolated fat containing cells.

of a large hard nodular tumor, about the size of an adult's head, filling the lower abdomen. The vaginal examination did not disclose the origin of the tumor. There was no ascites. At operation, a solid tumor of the right ovary was removed. The uterus and left adnexa were left in situ. There was no observation relative to the condition of the uterus, its size or succulence.

The specimen grossly is a nodular tumor measuring 11 by 7 by 6 cm. The surface is smooth and the consistency uniformly hard. A fibrous capsule surrounds

the growth. It cuts with difficulty, like a fibroma durum, and on section presents a striking appearance. In different areas of the tumor, mainly peripheral, are well demarcated yellowish areas of varying size from 2 cm. to 6 cm. in diameter. On close scrutiny these areas present small white glistening bands radiating from numerous points in the yellow areas (Fig. 8).

Occupying a large part of the tumor, about one half the total area, is a broad surface densely hard and almost pure white. It is striated and here and there a faint yellowish island of tissue can be identified.

Fig. 8.—Case 3, sixty-five years old. Vaginal bleeding, densely hard tumor showing discrete yellow nodules and massive hyaline connective tissue development.

Fig. 9.—Hyaline tissue with few connective tissue cells from dense area of tumor.

The gross appearance of the tumor is so peculiar that one immediately realizes that it is an unusual neoplasm probably desmoid in character. The fibrous nature of the growth is most striking.

On histological study two main elements stand out that aid in identifying the tumor. One is the marked production of connective tissue with a tendency to hyalinization or collagenous change (Fig. 9) and the second is the large masses of fat-containing epithelial cells that are present (Fig. 10). The yellow areas that were grossly conspicuous are composed of large spindle cells with blunted ends and

large oval centrally placed nuclei at times vesicular, at others darkly stained with a definite nucleolus. The cytoplasm is somewhat vacuolated and Sudan stains show these vacuoles to be fat globules. They vary in size, and while most of them are intracellular, globules are found between the cells.

The fibers run in bundles, which cross each other in no definite order, suggesting the interlacing arrangement of a cellular fibroma or fibromyoma. Often in the

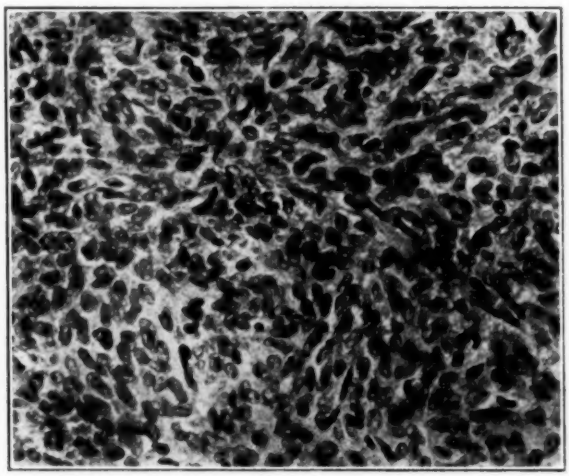

Fig. 10.—Spindle polygonal cells from yellow areas. These were fat containing cells.

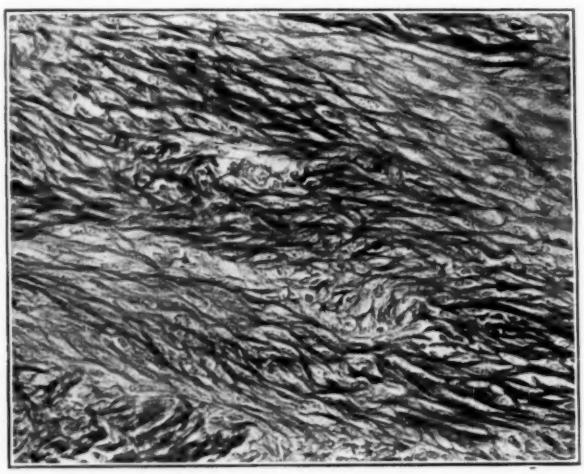

Fig. 11.—Massive fibrous tissue. Surrounding and compressing epithelial cells. These cells still contain fat.

midst of the cellular areas small islands of fibrous tissue can be found, and in addition bands of fibrous tissue are seen extending into the cellular areas. Close study of the cells in this region, by means of special stains, as Mallory, Van Gieson, and Bielchowsky, indicates that the connective tissue fibrils are closely associated with the epithelial cells, and not a replacement phenomenon due to degeneration. Fine fibrils seem to reach out from the cells, which fibrils surround the cells, fuse into larger, coarser strands and bundles, and then merge to form the collagenous islands

that contain the shadowy outline of a few cells or an occasional pale staining nucleus (Fig. 11). In these fibrous areas fat is found only in scanty amount. At the periphery of such a plaque, the fat is more prominent and in larger amounts. Löffler and Priesel have given an excellent description of the relation of the connective tissue to the epithelial cells and have expressed the opinion that this tissue is a product of the cells.

In the dense white areas the histological study demonstrates the structure to be almost entirely connective tissue showing collagenous areas. Here cells are very scanty in amount and fat is practically absent.

One gets the impression that the cells that compose the tumor have the function of accumulating lipoid material, and also of producing connective tissue or stimulating its growth. When the one function is in the ascendancy the other practically ceases. Blood vessels are numerous, especially in the cellular areas, where they are dilated, while in the connective tissue zone they are rare. Occasionally pigment is present in the endothelial cells of the vessels and in some of the fusiform cells. This is lipoid pigment that has accumulated in the cells.

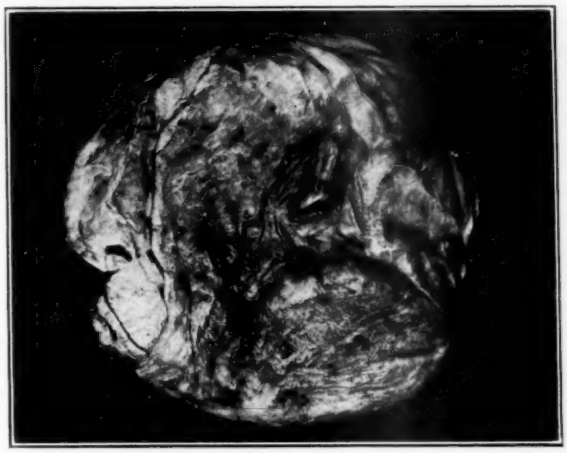

Fig. 12.—Case 4, fifty-nine years of age. Vaginal bleeding, thick wall cyst, bright yellow color, inner wall shaggy, contains blood.

CASE 4.—(Courtesy of Dr. A. A. Berg.) D. R., the patient was fifty-nine years of age, married and had three children. She had had a normal menopause seven years before and was admitted to the hospital with a history of severe lower abdominal pain and vaginal bleeding. There was a history of previous abdominal pain but no bleeding. The physical examination was negative except for the presence of the large tender fixed abdominal mass which by vaginal examination was diagnosed as a twisted right ovarian cyst. At operation a twisted hemorrhagic, right-sided, thick-walled ovarian cyst was removed. The uterus and left adnexa were left in situ. There was no observation noted relative to the size or condition of the uterus.

The specimen received in the laboratory was a collapsed thick-walled cyst, the wall measuring 1.5 cm. in thickness and of a bright yellow color (Fig. 12). The appearance of the wall was that of a tiger skin except that instead of a yellow and black striping it was yellow and white. In some areas the evidences of torsion were noted in the wall. The inner wall was shaggy in places, but no papillae were present. The original diagnosis was a twisted, fibro-xanthomatous cyst. However,

on further study, the wall showed the typical appearance of cellular islands composed of large fusiform and polyhedral cells with vacuolated protoplasm and containing lipoid. The connective tissue strands resembled those in the tumors already described. The tumor had been fixed in formalin and so hormone studies were not undertaken.

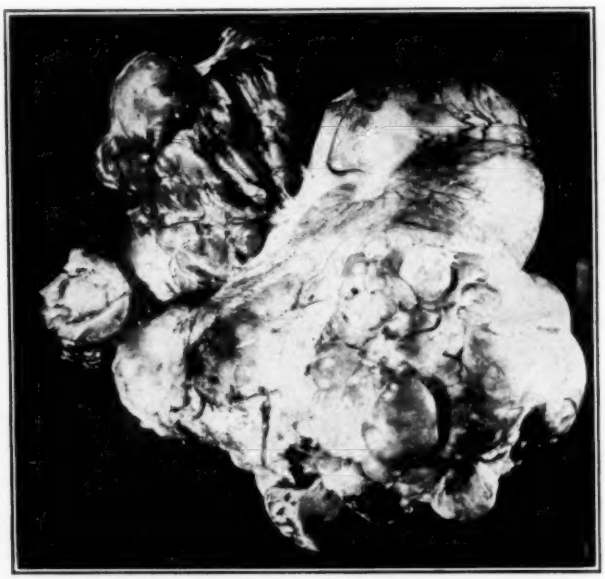

Fig. 13.—Case 5, sixty-five years old. No vaginal bleeding, multilocular serous cyst adenoma with densely hard yellowish white solid tumor near the center.

Fig. 14.

Fig. 15.

Fig. 14.—Showing connective tissue arrangement with fine fibrils extending into the cellular islands surrounding individual cells.

Fig. 15.—Fat stain showing distribution of fat in cellular islands.

CASE 5.—(Courtesy of Dr. A. A. Berg.) S. G. was a woman, sixty-five years of age. Her previous history was irrelevant. She had had a natural menopause fifteen years ago and there had been no further vaginal bleeding, Recently she had noticed a gradual enlargement of the abdomen and some edema of the legs.

The physical examination was negative except for the presence of a large abdominal mass reaching almost to the ensiform. There was some edema of the legs. She had evidence of a chronic nephritis. A diagnosis of an ovarian cyst was made and at operation a large cystic tumor of the left ovary was removed with the slightly enlarged uterus and right tube.

Grossly the specimen consisted of a uterus and left ovarian mass. The uterus was slightly larger than normal in size, the endometrium pale, thickened, granular and from the left cornu a polyp 2 cm. in length projected. The ovarian mass consisted of numerous grapelike large cysts, smooth, bluish in color and at one point a solid mass 5 cm. in diameter was present (Fig. 13). The solid tumor presented

Fig. 16.—Hyperplastic endometrium, associated with theca cell tumor in a woman sixty-five years of age (Case 5).

a yellowish white color with pearly white septa traversing its cut surface. There were also a number of small cavities at one pole. The cysts were thick walled and contained a thick yellowish green mucoid material. In two of the larger cysts small granular hemorrhagic excrescences were found.

The histologic examination demonstrated that the cysts were typical multilocular, benign serous cysts.

The solid tumor was made up of cellular islands composed of plump spindle cells separated by connective tissue bands and masses. The connective tissue fibrils in places extending into these islands and separating the individual cells (Fig. 14). There was a definite tendency for the connective tissue to be hyalinized and small plaques could be found.

The cellular islands contained a large amount of double refractile fat globules and only a very scanty amount was present in the connective tissue (Fig. 15). The uterine mucosa histologically was hypertrophic (Fig. 16), and the polyp presented the same histological pattern.

## DISCUSSION

The published cases of Löffler and Priesel, of Melnick and Kanter and of our own permit us I believe to classify this group of tumors as a definite clinical and pathological entity.

Clinically these tumors are unilateral neoplasms occurring commonly after the menopause. In three cases of the seventeen they occurred before the menopause, two published by Löffler and Priesel, and one of our cases.

Aside from the symptoms of any pelvic neoplasm these tumors present in most instances a definite and clear-cut syndrome. The most striking symptom is atypical bleeding, usually postmenopausal as this is the common age of tumor occurrence.

In one of our patients twenty-one years old there had been a history of bleeding for a year with a short period of amenorrhea following the bleeding. In a case of Löffler and Priesel, aged eighteen, a similar history was obtained. In addition one patient noted an enlargement of the breasts. The uterus was enlarged and soft and in the cases where the endometrium was examined it was found hyperplastic. Endometrial polyps were found in several cases. After the removal of the tumors the symptoms regressed.

While in one instance Löffler and Priesel report a case as malignant all the others thus far observed apparently have remained well after operation.

The gross and histologic appearance is most striking and characteristic. The tumors are hard, somewhat nodular growths that may reach the size of an adult's head. They suggest a fibroma in consistency and appearance, but unlike fibromas are not accompanied by ascites. Löffler and Priesel report one case with 250 c.c. of ascitic fluid. However, the tumor may be represented by a large degenerated cystic mass as in one of our own cases (Case 4), previously diagnosed a twisted fibroxanthoma, or may be associated with other growths as Case 1 with a dermoid and in Case 5 with multilocular serous cysts. On section the cut surface is distinctive. The color is usually yellowish white, this being due to the presence of varying sized yellow cellular islands separated by finer or coarser hyaline connective tissue bundles. The connective tissue may be so massive in amount that the cut surface of the tumor may exhibit white hyaline areas containing only tiny pinhead sized islands of light yellow color, and in addition may be studded with a few or many larger isolated nodules of deep yellow tissue surrounded by the hyaline masses. Small hemorrhagic areas are found and at times small sized cysts that may reach the diameter of a walnut. These cysts may coalesce and form larger cysts.

Histologically these tumors present a characteristic picture. The yellow areas are composed of plump spindle or polygonal cells with

a central or at times an excentric elongated or irregular nucleus, dark staining and rich in chromatin. The cells have an epithelioid appearance. The cell protoplasm is vacuolated and contains fat (Figs. 4, 17, and 15). The fat globules may also be present in the interstitial tissue to some slight extent but only when cells are still present. The fat then is usually found at the periphery of the connective tissue plaques and strands and these fat globules are very tiny in contradistinction to the large globules and masses in the cells. Pigment granules are occasionally present in the epithelioid cells. Blood vessels are present but not in great number. They appear both as fine capillaries and as large vessels. They are found in the connective tissue capsule and at the periphery of the cellular islands. The vessel endothelium contains pigment granules (lipochrome).

The connective tissue bundles are hyaline to a great extent, and often large hyaline plaques are present in the midst of a cellular island with fibers extending out radially and surrounding the individual cells or seeming to enter them.

The fibrous tissue bundles vary in size, density, and structure. They may be very fine, composed of but a few fibrils or so massive as to represent the greater part of the tumor. They may be composed of a few connective tissue bundles or large masses of hyaline tissue. Connective tissue cells are usually scanty in number and in some of the fibrillar meshes isolated cells resembling the true tumor cells and containing fat are found. The connective tissue bundles run in a criss cross net work surrounding the cellular areas. Finer fibrils may encircle cell groups or even individual cells. It seems that where the connective tissue is actively proliferating it throttles the growth of the epithelioid cells.

The cysts as previously mentioned are probably degenerative in origin. The walls may be smooth or as in the large one previously described shaggy. The contents are a yellowish clear or turbid fluid containing cholesterin crystals, fat droplets and cellular débris. There is no definite lining though occasionally a flattened endothelial-like row of cells is found in scattered areas.

In addition to the characteristic clinical and pathological picture above described these tumors present other definite features. The chemical study as well as the microchemical and polariscopic investigation demonstrates that these tumors contain fat. The fat to a great extent is cholesterol and cholesterolester and not degenerative in nature. It is limited almost entirely to the cellular elements comprising the tumor and is found only in tiny scattered globules in the connective tissue. In the granulosa cells as pointed out by Melnick and Kanter the fat is usually phospholipid, while here the greatest amount of lipoid was in the nature of cholesterol and cholesterolesters.

Melnick and Kanter suggested on purely hypothetical grounds the possibility that these tumors were able to produce an estrogenic hormone. Dr. Frank Spielman examined one such tumor for its estrogenic hormone content and found that the tumor contained one mouse unit per 0.75 gm. of tissue extracted. This demonstrates that these tumors can produce or store an estrogenic hormone. The investigation of various other solid and cystic tumors of the ovaries failed to demonstrate the presence of an estrogenic hormone except in follicular cysts as demonstrated by Robert T. Frank, and in the granulosa cell tumors as shown by Salmon by extraction and by R. Meyer and others by implantation. It has been found in uterine tumors and other tissues in small amounts.

To recapitulate: We have described a group of five tumors that have definite clinical, pathologic, hormonal and chemical characteristics. They are differentiated from fibromas or fibrosarcomas by the mottled yellow appearance due to the cellular islands separated by connective tissue and the absence of ascites. Apparently the growth is the product of a cell type that has the potentiality of not only reproducing its type but of forming connective tissue fibrils or stimulating the intercellular substance to become fibrillar.

The removal of the tumor causes a cessation of the clinical signs and a regression of the abnormal findings. This suggests that the hormone content may play a rôle in producing the signs and symptoms of the disease.

The theca interna cells of the ovarian parenchyma can produce or store an estrogenic hormone, and can produce or store lipoid. They also stimulate the formation of connective tissue which has a tendency to hyalinization as noted in the regressive follicle or corpus atreticum.

While the granulosa cells to a certain extent have similar properties there are sufficient points of difference to enable us to separate the granulosa cell tumors from the theca cell tumors.

The gross appearance of the two tumor types is distinctly different, the theca cell tumor being a hard, fibrous yellow growth whereas the granulosa cell tumor is a more cellular, medullary, softer neoplasm. Nowhere in the theca cell tumors does one find areas suggestive of the morphology or pattern of the granulosa cell tumor. The former is a much more uniform tumor. The lipoid distribution in the granulosa cell tumors differs from that in the theca cell tumor.

The clinical symptoms are similar, but with cells having such closely allied biological properties it is but natural to expect the same clinical picture. In none of the seventeen cases do we find the tumor in children whereas Klaften has reported that 8.9 per cent of granulosa cell tumors occur before puberty. Furthermore while granulosa cell tumors occur in 48.8 per cent after the menopause in this group of seventeen cases 83 per cent occurred postmenopausal.

Because of the histologic, chemical and biological resemblance of these tumor cells to the theca interna cells of the ovarian parenchyme it is suggested that the theca interna cell forerunners in the ovary are histogenetically involved.

REFERENCES

*Fischel, A.:* Ztschr. f. Anat. **92:** 34, 1930. *Frank, R. T.:* J. A. M. A. **78:** 181, 1922. *Geist and Spielman:* J. A. M. A. **104:** 2173, 1935. *Löffler and Priesel:* Beitr. z. Path. Anat. u. Allg. Path. **90:** 199, 1932; Wien. med. Wchnschr. **84:** 400, 1934. *Melnick and Kanter:* Am. J. Obst. & Gynec. **27:** 41, 1934. *Schiller:* Path. u. Klinik. der Granulosa zellentumoren, Wien, Maudrich, 1934. *Werdt, V.:* Beitr. z. Path. Anat. **59:** 453, 1914. *Zondek:* Die Hormone des Ovariums und des Hypophysen Vorderlappens, Berlin, 1931. *Sobottka, Epstein, and Lichtenstein:* Arch. f. Path. **10:** 677, 1930. *Kuttner and Cohen:* J. Biol. Chem. **575:** 516, 1927.

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## SOME NEWER ASPECTS OF REPRODUCTIVE PHYSIOLOGY

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IT IS not the purpose of this paper to present a review of recent advances in the field of reproductive physiology, but simply to discuss a few, chosen because of their newness, their importance, and their bearing upon clinical problems. The paper thus deals with trends rather than with individual studies. The literature of reproductive physiology is vast and widely scattered. Many of the most important publications appear in nonclinical journals, so that their contents only slowly reach the current of gynecologic literature. No one person can possibly view the entire changing panorama in the intensively worked field of endocrinology, while the average busy clinician is likely to be so bewildered that he dismisses it all as a hopeless muddle.

It would seem, therefore, that there is a genuine justification for papers which aim at summarizing, simplifying and appraising the rapidly growing knowledge in this general subject, which is so full of potentialities in its application to our clinical problems in gynecology. We would be very short sighted if we allowed our interest to lag merely because thus far so little has been accomplished in the application of reproductive endocrinology to our many problems of treatment of functional diseases in women. In the present state of our knowledge, I personally am far more interested in endocrinology than in organotherapy. To assume the "practical" futility of the former would be just as foolish as to deny the usefulness of a knowledge of the pathology, life history, and general characteristics of such a disease as cancer, just because we do not as yet have a very satisfactory treatment for it.

For this discussion I have selected four subjects which impress me as being timely, important, and perhaps not quite so familiar to most clinicians as they should be. They are (1) the newer studies on the chemistry of the sex hormones; (2) the possible participation of the posterior lobe and the parahypophyseal portions of the midbrain in the reproductive cycle; (3) the question of so-called anovulatory menstruation; and (4) the endocrine factors in menstrual bleeding.

A host of other topics invite discussion. For example, it would be of interest to say a word concerning the bedeviling new concept of antihormones, but this is still so nebulous and so unconfirmed that no worthwhile conclusions can as yet be drawn. Again, it might be of interest to include a discussion of the newer work on the physiology of lactation, the elucidation of which is almost entirely due to the work of American investigators, and also the newer developments concerning the effects, normal and abnormal, of the ovarian hormones upon the mammary gland. But considerations of space necessitate selectiveness, and only the few subjects indicated above will be considered in this paper.

## THE CHEMISTRY OF THE SEX HORMONES

To my mind, the most outstanding development in the field of reproductive physiology during the past few years has been the recent work on the chemistry of the sex hormones, and especially the demonstration of the close kinship in the molecular structure of the male sex hormone, the follicular hormone and progestin, as well as the remarkable relationship of all three of these to the well-known sterol group of chemical compounds, to the the bile acids, to certain vitamins, and to various carcinogenic substances. When one considers that only a few years have elapsed since the discovery (1927), by Aschheim, that estrin is present in large amounts in urine of pregnancy, and that up to the opening up of this large source, chemical studies of the hormone on any large scale had hardly been possible, one can appreciate the rapidity with which our knowledge has been advanced since then. Within a few years estrin was obtained in crystalline form by Doisy and his coworkers, the crystals being for the first time exhibited by Doisy at the International Congress on Physiology, held at Boston in August of 1929. At about the same time, and quite independently, a similar accomplishment was achieved by Butenandt, whose publication appeared a little before that of the American workers. Still other investigators reported similar results almost immediately afterward, indicating what a hot trail all had been following.

It soon became apparent that not all of these studies had yielded exactly the same substance, but that estrin existed in a variety of forms, so that soon it became necessary to distinguish between ketohydroxyestrin ($C_{18}$ $H_{22}$ $O_2$) and trihydroxyestrin ($C_{18}$ $H_{24}$ $O_3$). The former is the

substance isolated by Doisy, and also by Butenandt, while to Marrian is due the credit of isolating the latter. Both occur in the urine of pregnancy, but ketohydroxyestrin is a far more potent physiologic substance than is the trihydroxyestrin. There are various other differences between the two, as regards methods of extraction, solubility and so on, but these need not be discussed here, especially as the present writer makes no pretense to the chemical knowledge necessary to do this intelligently.

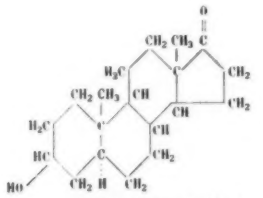
There are still other forms of estrin described (the alpha, beta and delta forms, equilin, hippulin, etc.), while almost nothing is known of its fate in the body. It has even been suggested that the estrin found in the urine of pregnancy is not identical with the estrin produced by the ovaries. There are many other unknown factors, such as our uncertainty as to how much estrin is produced in the body, how much is taken in with food, how and in what chemical form it is utilized by the organs, and how much of it is destroyed and where, so that really we can determine only how much is eliminated. Even this, as Siebke emphasizes, is inaccurate, for such determinations deal with definite amounts obtained by one technic or another, with no certainty that this reflects the amount of original hormone present in the blood, and perhaps not indicated by the technic employed. We do not know whether all of the variants of estrin are essential for the female cycle, or whether they represent only excretion derivatives. This confuses blood and urine hormone studies a great deal, especially as there is the widest variation in the potency of the various forms of estrin. For example, as Schoeller says, if $\alpha$ (alpha) folliculin is excreted as the hydrate, with a drop in potency from 8 or 10 million mouse units to 75,000 units per gram, it can be seen that interpretations based on the urine hormone output would necessarily be very erroneous.

As regards the chemistry of the corpus luteum hormone (progestin), there has been the same intensive pursuit of its structural formula, the pioneers being Allen, Butenandt, and Slotta, Ruschig and Fels. Butenandt gives its chemical formula as $C_{21}$ $H_{30}$ $O_2$, and he, with Westphal and Hohlweg, in April of 1934, described the preparation of a crystalline chemically pure substance with this formula. Here again there are a group of closely related substances to be dealt with.

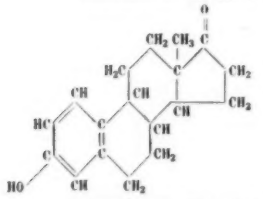
My purpose in discussing the chemistry of these hormones, however, is to emphasize, first, a fact which may prove to be of great clinical importance, viz., the close structural relation which exists between the two ovarian hormones and between them and the male sex hormone, ankrokinin or androsteron. This is at once evident from the fact that all three of these hormones are built up around the same phenanthrene group, composed of 3 six-membered rings. Phenanthrene itself, rather curiously, is quite inactive, but the various sex hormone derivatives possess various types and degrees of physiologic potency.

Long before these fundamentally important facts had been established, it seemed logical to believe that there must be some very close relationship between estrin and progestin, for both are products of essentially the same cell. Just as the lutein cell is only a modified granulosa cell, so it seemed that progestin would prove to be only a modified estrin. This, indeed, is what actually seems to be the case.

Just as surprising as the relation between estrin and progestin is that which exists between the male and female sex hormones. It has long been known that estrin is at times found in the urine of men, and the male hormone in the urine of women. As a matter of fact, perhaps the most surprising feature of Siebke's recent thorough study of the hormone excretions of women during the menstrual cycle is the constant finding of the male hormone in the urine, though not in the feces. From a quantitative standpoint, the amount is not at all negligible, a liter of



Androsteron $C_{19}H_{30}O_2$



Follikelhormon $C_{18}H_{22}O_2$

Formula 1.—Showing the structural chemical similarity between the male hormone (androsteron) and the follicle hormone. Note in each the three hexagonal rings of the phenanthrene nucleus (Butenandt).

urine containing an amount of the male hormone worth in Germany 10 R.M., at the present marked value of the substance. Indeed, Siebke suggests female urine as a conveniently available source for the production of the hormone. A more striking incongruity is seen in the case of horses, for the urine of both the mare and the stallion is rich in estrin.

While the finding of the male hormone in women might theoretically be explained as due to the secretory activity of the potentially testicular elements normally present in the region of the rete ovarii in all women, and while this explanation is still favored by some, it is difficult to explain on corresponding histologic grounds the presence of the female hormone in the urine of males. It seems more likely that the reason is to be sought in the recently demonstrated closeness of chemical relation between the male and female principles. Again we see in each the same phenanthrene nucleus, and the molecular formula of the male hormone

differs from the female only by a molecule of water and an atom of carbon. Zondek has recently suggested that in both sexes the male hormone is first produced, being converted by dehydration into the female, probably under the influence of the metabolic processes which many consider to be of underlying importance in the matter of sex determination. This explanation would obviously not apply to the paradoxical conditions existing in the equine family above alluded to.

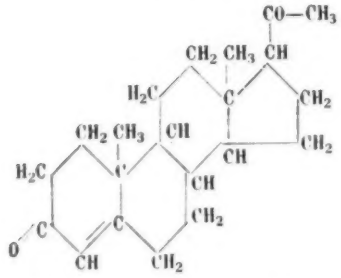
It will thus be seen that this newly discovered chemical relation of the male and female hormones is of fundamental importance as regards the questions of sex specificity, sex differentiation, and intersexuality. More and more evidence is accruing to show that the cells of either sex type of gonad are capable of producing either male or female hormones. As just one instance may be mentioned the cases of intersexuality which are characterized by dominantly female characteristics even though the only gonads present are testes. This is illustrated in a recent case of my own, more fully described in a paper recently presented before the Section on Pathology and Physiology of the American Medical Association. It is also well exemplified in the recent case of similar nature reported by Cadiz and Lipschütz, in which typical menopausal symptoms followed removal of the patient's testes. There is a considerable mass of evidence to the same effect available from the experimental laboratory.

It requires no great stretch of imagination to conceive of the possible bearing of such observations upon the production of intersexual conditions, particularly if one accepts the viewpoint championed by Witschi, and favored by many biologists, that the cortex of the gonad is a determiner of femininity and the medulla a determiner of masculinity in the germ cells. In other words, a germ cell developing in the cortex will become an oöcyte, that in the medulla a spermatocyte. This has been clearly established in such animals as the frog, and there is much to support it as regards the higher forms. If such facultativeness is exhibited by the dominating germ cells themselves, it would not be surprising if the character of the sex hormones also were susceptible of modification by environmental conditions.

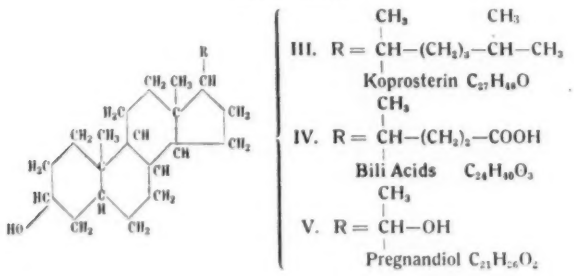
The immediate advantage of securing the sex hormones in pure form is that it will make possible more precise study of their physiologic rôles. By contrast, the inability to prepare the various anterior pituitary hormones in pure form has been the greatest handicap in the study of their physiologic action, not to speak of their therapeutic application. Again, it has already been shown that the potency of estrin preparations is susceptible of enormous increase by means of chemical treatment, and there is even a strong possibility that they may, before very long, be produced by synthesis. A hopeful start along this line has already been made by Butenandt and others.

Just what factor it is which in the mechanism of the reproductive processes determines the transformation of estrin into progestin, if such a transformation does occur, cannot be stated, though the obvious suggestion would be that it is dependent upon the interrelationships between the ovarian and pituitary functions, just as this interrelationship apparently determines the transformation of granulosal into lutein cells. Not only in the normal mechanism but also in certain pathologic conditions is there seen such a transformation of granulosal into lutein morphology and function.

For example, in the well-known granulosa cell group of ovarian tumors, one may occasionally find a metamorphosis of granulosa cells into lutein-like cells (granulosa cell carcinome lipidique), and this change



Formula 2.—Structural formula of the corpus luteum hormone or progestin (Butenandt).




Formula 3.—Showing close relationship between koprosterin, the bile acids, and pregnandiol, an estrogenic substance found in the urine of pregnant women (Butenandt).

in morphology is reflected in the appearance of a decidual or predecidual picture in the endometrium. Such an endometrial response cannot, so far as we know, be brought about by any factor save progestin, and there would seem to be no other source for the latter except the modified granulosa cells. In a case of this type recently reported by Novak and Brawner, the patient was ten years beyond the menopause, and there were, of course, no functioning corpora lutea in the ovaries.

There is still another angle of this new chemical work which has excited intense interest among investigators. I refer to the discovery of the close chemical relation which apparently exists between the sex hormones and the well-known sterol group of chemicals, and particularly the so-

called carcinogenic substances, such as certain tar derivatives. Here contact is made with the most important of medical problems, that of cancer in general, and the rush of investigators to this new line of approach is ample evidence of the possibilities which it is believed to offer.

With the sterol substances, including cholesterol, as with the bile acids, we have again to deal with the same three hexagonal rings of the phenanthrene nucleus which characterizes the three gonadal hormones. Curiously enough phenanthrene itself is inert so far as any biologic effect upon the genital tract is concerned. On the other hand, as Dodds and others have shown, certain of the sterols, when injected into castrated female animals, bring about definite estrous effects. This rather startling observation would make us question the specificity of the hormones to which alone such biologic effects have hitherto been ascribed. It would also seem to throw light on the occurrence of estrogenic principles in various bituminous minerals, and in coal, peat, petroleum, and crude oil. The presence of biologically potent chemicals seems to offer a more probable explanation for this than does the view that these substances contain the locked-up and still active female sex hormone existing in the plant life of millions of years ago. That hormones play an important part in plant life is now apparently well established.

Most provocative of all, however, is the fact that certain of the sterol substances are not only estrogenic but also carcinogenic. There are a certain number of circumstantial observations which even before this had suggested some sort of relation between the endocrine organs and cancer, such as the frequent positiveness of the Aschheim-Zondek test in cases of female genital cancer, and the finding of large amounts of estrin in the blood of cancer patients, even when these are males. To these might be added the results of many experimental studies during the past few years, such as those of Murray, Cook and Dodds, Overholser and Allen, Hofbauer, Geschickter, Lewis and Hartman, and Lacassagne. The last named, for example, has reported the production of mammary cancer in three male mice, in a strain in which this disease spontaneously affects only the female, by means of the injection of oily solutions of estrin.

To say, as some are already saying, that cancer is perhaps produced by derivation or deterioration products of the hormones, is certainly unjustified and premature, but, on the other hand, the possibility that the closed door of cancer may sooner or later be unlocked by an endocrine key has been made more real by the chemical studies we have been discussing. On the other hand, it is only fair to state that some investigators, notably Loeb, are considerably less enthusiastic about the possibilities in this field. In his recent review of the subject, this author states that "while carcinogenic hydrocarbons as well as regenerative processes (irritation) may affect a great variety of tissues, the estrogenic

hormones are limited in their action to the tissues in which they induce growth processes during the normal sexual cycle." In any event, the next few years are sure to be exciting ones to those now pushing forward along this new line of investigation.

### THE PARTICIPATION OF THE POSTERIOR HYPOPHYSEAL LOBE AND THE MIDBRAIN IN THE CYCLE

In all discussions of the mechanism of menstruation, it is upon the endocrine factors that much the heaviest accent has been laid, first those originating from the ovary, more latterly also those arising in the anterior lobe. Indeed, almost nothing is known of any other cogs in the menstrual machinery, though some must be of great importance. It is of interest, therefore, to note that physiologists are now probing deeper than the anterior hypophysis in the elusive search for the "deus ex machina" of the reproductive cycle. We must now encompass in our discussions of the subject at least a nebulous consideration of the probable rôles of the posterior pituitary lobe, the hypothalamus, and the floor of the third ventricle, and already a sexual center, located somewhere in the midbrain, has been postulated.

Perhaps the first intimations that the parahypophyseal portions of the midbrain play a part in the reproductive cycle emanated from the long discussion as to the seat of disturbance in certain abnormalities of the cycle, and especially in the so-called hypopituitary amenorrhea associated with the adiposogenital dystrophy of Fröhlich. This is not the place to review the fluctuations of the discussion throughout many years. Suffice it to say that there now seems to be general acceptance of Smith's convincing demonstration that the metabolic disturbances of this syndrome are of hypothalamic and not of pituitary origin, though the anterior hypophysis is responsible for the sex changes.

The exact nature of the hypophyseocerebral relationship is not known, and certainly there is no widespread acceptance of the view that the mingling of effects is due to an invasion of the hypothalamus by hypophyseal cells. At any rate, we can no longer hew too closely to the hypophyseal line in the consideration of the metabolic disturbances which are so often associated with amenorrhea. There is as yet no evidence, however, to indicate that an extrahypophyseal factor may be concerned in the frequent transitory weight increase of the normal human cycle. Attention has been recently called to these by Sweeney, as a result of weight studies of 42 normally menstruating women. In 30 per cent of these, he found an increase of 3 or more pounds during the period.

My own experience convinces me of the general correctness of Sweeney's observations. I have been especially interested in the group of cases first described by Thomas in 1933, in which the menstrual weight

increase was exaggerated, and was obviously due to a generalized edema. I have seen four such cases in the past two years. In one of these the gain of weight was as much as fifteen pounds, and the edema during the menstrual period was very obvious, with swelling of the face tissues, puffiness of the eyelids, and swelling and pitting of the feet and ankles. In two of the patients in whom there was an opportunity for fairly complete study, it was easy to demonstrate marked fluid retention during menstruation, with polyuria and rapid disappearance of the edema after the period.

Of especial interest was a patient of twenty-one who suffered with complete amenorrhea of three years' duration, together with enormous adiposity, her weight being 232 pounds. She responded quite favorably, so far as weight was concerned, to a low caloric diet, together with the administration of moderate doses of thyroid, even though her basal metabolism rate was very little below normal. Her weight dropped to 185 during the period of several months she was under observation, but this drop in weight was punctuated by sharp rises of from seven to ten pounds occurring rather regularly at three-week intervals. It was not uncommon for this patient, almost over night and with no intake of fluid or food, to show this sharp rise of weight, and this was accompanied by a lowered output of fluid and visible evidence of mild edema. In other words, she exhibited a three-week metabolic cycle even though there was no cycle of menstrual bleeding. At the end of four months, and possibly as a result of light hypophyseal radiation, she began to menstruate, her periods of bleeding coinciding with the weight increase.

A search of the literature has shown the meagerness of our knowledge concerning this interesting phenomenon of menstrual edema. It presents some points of similarity and some of dissimilarity to the so-called Epstein nephrosis, which, however, is not a cyclic phenomenon. The first and almost the only laboratory studies of the subject appear to be those of Eufinger and his collaborators. In Eufinger's first paper, in 1928, he found that 30 per cent of normally menstruating women exhibit a lessened stability of the blood colloids. In another paper of the same year, with Goldner, it was shown by studies of the blood proteins that during menstruation there is a sharp rise in the level of globulin, which may be even doubled, while the albumin level drops correspondingly. Usually by the end of menstruation the globulin content has again dropped to normal, and the albumin has risen to its former level.

In a third paper, with Spiegler as collaborator (1928), based on a study of twenty-five normally menstruating women, he presents evidence to indicate that this physicochemical disturbance of colloid structure is linked up with water metabolism, leading to water retention during menstruation. Incidentally, as Eufinger and Spiegler show, there has been much difference in the results of studies upon a possible chloride

retention during menstruation. In 47 per cent of the cases studied, these authors demonstrated a water retention and tendency to edema during menstruation and at times during the immediately premenstrual period.

In these days of endocrine explanations, it is hard to avoid thinking of the posterior lobe as in some way linked up with this phenomenon of cyclical water retention, and of theorizing that this structure, so overshadowed in gynecologic interest by the anterior lobe, may participate in the cyclical changes of menstruation, and that in some way its admittedly antidiuretic function is increased during menstruation. The problem is, of course, not so simple as all this, as one will soon learn if one begins to look into the intricacies of water balance. A very superficial peep was enough to discourage me from attempting any discussion of this problem.

My reason for including the subject in this paper was simply to stress the fact that in the endocrinopathic weight increases so frequently observed in gynecologic practice, one must take cognizance not only of a metabolic disturbance characterized by actual deposit of fat, but also of the factor of water and possibly chloride retention, manifested in some degree even in many normally menstruating women and to a more striking degree in the occasional cases of generalized menstrual edema. It is quite certain that these two types of disturbance may coexist in the same patient.

From what has been said, it will be seen that there is considerable justification for the view that the cycle of menstruation involves not only the endocrine glands, but that certain areas of the brain are involved also. Still other evidence along this line is available in the recent studies of Hohlweg and Junkman upon the reverse effect of the follicle hormone upon the anterior lobe. The work of Kunde, d'Amour, Carlson and Gustavson, that of Meyer, Leonard, Hisaw and Martin, Moore and a host of other investigators, have established the fact that continued injection of sufficiently large doses of estrin brings about inhibition of the anterior pituitary sex hormone function. This general conclusion is not invalidated by the recent paper of Clauberg and Breipohl, in which it appeared that a single large injection of estrin was followed by a sharp increase in anterior pituitary activity. The latter conclusion, moreover, still needs confirmation.

The special interest of the contribution of Hohlweg and Junkman lies in their conclusion that the inhibition of the anterior lobe is not a direct one upon the gland, but that it is mediated through a sex center in the midbrain. If, for example, a second hypophysis is implanted into the kidney and the animal later castrated, only the normal hypophysis and not the implanted one shows the well-known castration changes. The conclusion therefore is reached that the effect on the normal pituitary is not a direct blood borne one, but that it must be exerted through

nervous channels, affecting the normal gland but not the implanted one. Hohlweg and Junkman therefore conclude that there must be a "sex center," located in all probability in the floor of the third ventricle, as indeed had been previously suggested by Teel and Cushing as a result of the study of the effects of tumors in this region. Schoeller suggests that this concept would explain the fact, first demonstrated by Philipp, that the hypophysis of the pregnant woman contains so little of the gonadotropic principles in spite of their abundance in the urine.

In all these studies there is manifest a strong new trend to seek beyond the endocrine glands for an explanation of the phenomena of the

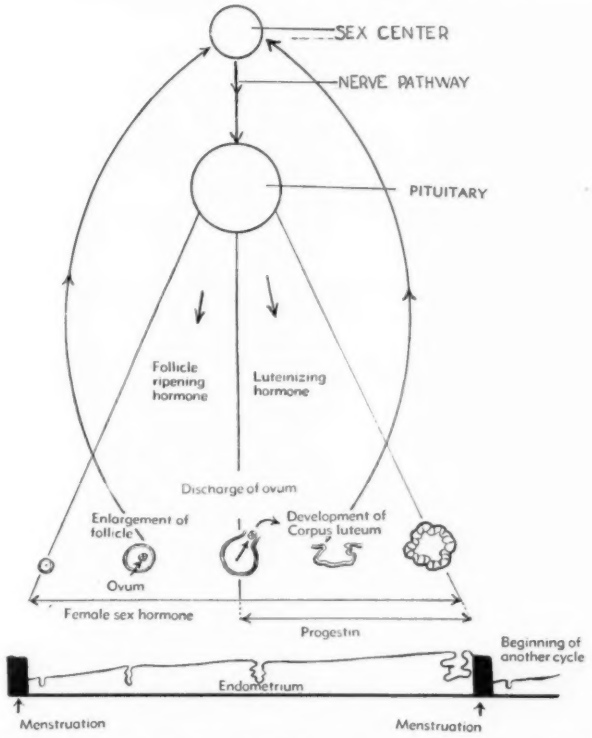



**Fig. 1.—Showing the probable mechanism by which the reverse inhibitory effect of the gonads upon the anterior hypophysis is produced, i.e., through the agency of a "sex center" in the midbrain and nerve pathways to the anterior lobe. (Adapted from Hohlweg and Junkman.)**

menstrual cycle, as if there were not enough factors already to bedevil and confuse those trying to keep up with the march of developments. As shown in Fig. 1, we must now add another link to the diagrams which have become so popular in the representation of how menstruation is brought about.

The chief significance of this extension of viewpoint would seem to be that it, for the first time, links up the endocrines and the nervous system. That they are closely coordinated has always seemed certain

on mere a priori grounds, for both are parts of the body's system of intercommunication, one primitive, the other highly developed. Even psychic factors have been generally accepted as possible causes of menstrual disturbances, and a beginning has apparently been made in exploring the pathways involved. Again, we may quite possibly have advanced a few steps toward an explanation of the vasomotor phenomena of the menopause, associated as they are with certain hormonal body changes, and yet so clearly involving nerve pathways. And the examples might be multiplied.

### THE ANOVULATORY TYPE OF CYCLE

The possible occurrence of a periodic uterine bleeding which clinically is indistinguishable from menstruation, but which is not associated with ovulation, is now established beyond all doubt. The early work of Corner, abundantly confirmed by Hartman and Allen, had shown that the anovulatory type of cycle is very common in monkeys, which resemble the human being quite closely so far as the reproductive mechanism is concerned. Van Herwerden had, indeed, maintained this possibility as far back as 1906. Some years ago Corner urged that this anovulatory type of cycle is found also in some women, though unquestionably in the vast majority ovulation and corpus luteum formation play essential rôles in the menstrual cycle. When, in 1934, as in several previous papers, I likewise emphasized the possibility of human menstruation without ovulation, and urged this as the explanation of some cases of sterility, a miniature international discussion was precipitated by Shaw, of London, who very generously diffused his criticism of my own views so as to include the distinguished laboratory investigators whom I have named above.

Since then a continuation of my own studies, as well as investigations in other large clinics, has conclusively shown the not infrequent occurrence of the anovulatory type of menstrual cycle. Tietze, from Schröder's clinic at Kiel, reports finding it in 31 of 466 cases of periodic bleeding. Mazer and Ziserman report the finding of a non-nidatory endometrium in twenty-four of forty-one regularly menstruating but functionally sterile women, a proportion much greater than I have encountered in my own work. Other authors reporting a considerable incidence of anovulatory cases are Fluhmann and Morse, Adler, and Anspach and Hoffman.

What is the mechanism of the menstrual cycle in these cases in which ovulation is lacking? Just after a menstrual bleeding, a group, probably a considerable group, of follicles begins to mature and soon to produce increasing amounts of estrin, just as in the usual ovulatory mechanism. Unlike the latter, however, rupture of a single follicle which has outstripped its fellows fails to occur. In some cases, it is true, there is a single dominating follicle, often becoming large and cystic, as one

not infrequently finds in cases of functional bleeding associated with hyperplasia of the endometrium. In other cases, and I believe even more frequently, one finds a considerable group of follicles developing to various stages without actually reaching full maturity, though all of them produce estrin. In the latter group one finds the small multiple cysts which are so often seen in the ovaries of the functional bleeding group. The important defect is in the ovulating principle, whatever this may be. The evidence points more and more to the probability that ovulation is produced, not by any one pituitary or ovarian principle, but that it occurs at a "drehpunkt" which is produced by a delicate quantitative balance between various hormonal factors.

In the typical functional bleeding case, the follicle is likely to develop, without rupturing, beyond the stage of usual maturity, after which a dehiscence sets in, with death of the ovum, degeneration of the granulosa, and cessation or marked diminution of estrin production. This is followed, after a variable number of days, by bleeding, most frequently an interval longer than normal because of the lengthened life span of the follicle. But this is not invariably so, for the retrogression of the follicle may begin sufficiently early to make the intervals between bleedings quite like those of menstruation, while the amount and duration of the bleeding likewise may resemble that of normal menstruation.

Thus is produced a periodic bleeding which, as I have said, is indistinguishable from normal menstruation, though at times there is some irregularity and some excess above the usual menstrual amount. Bleeding of this type is, in my experience, most often encountered in women approaching middle life, as well as in young adolescent women, though it may be seen at any age during reproductive life. The age distribution, in other words, is quite like that of functional bleeding, of which it may be considered a mild form. Whether or not it is always to be considered pathologic, even when menstruation is ostensibly proceeding normally, is a matter of definition. There is no possible way of distinguishing this type of cycle clinically from the usual ovulatory type except by microscopic examination of the endometrium, and this should be done when there is some clear clinical need for such information, as in cases of sterility in which all other factors have been ruled out.

The endometrium will yield the necessary information only if studied shortly before an expected flow. In the usual ovulatory cycle there is then present in the ovary a large, functioning corpus luteum, producing progestin, and bringing about the characteristic secretory phenomena in the endometrium. If, however, the endometrium shows only one type or another of proliferative endometrium, with no evidence of secretion, one may conclude that there is an absence of progestin, that no functioning corpus luteum is present in the ovary, and that therefore ovulation has not occurred. Usually the distinction between the secretory and non-

secretory types of endometrium is possible from histologic examination alone, although it can, and usually should, be confirmed by differential staining for glycogen.

A typical case of this group is represented by the patient whose endometrium is shown in Fig. 2. She is twenty-eight years old, and both she and her husband have been repeatedly examined and found normal by competent clinicians in New York and Baltimore. The couple had been married seven years, with no pregnancies. Menstruation, the dates of which had been carefully recorded for many years, recurred at quite regular thirty-day intervals, the flow lasting five days, and being moderately free. By way of parenthesis, I may add that, like many others, I am very skeptical of the accuracy of menstrual dates unless properly recorded by the patient. An aspiration curettage done on the

Fig. 2.

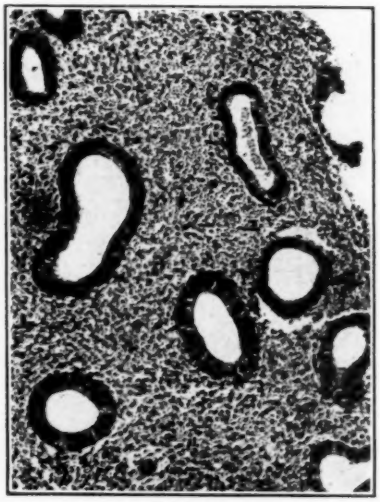


Fig. 3.

Fig. 2.—Proliferative, nonsecretory endometrium obtained by suction-curette from uterus of a sterile woman of twenty-eight years on twenty-ninth day of thirty-day cycle. (See text.)

Fig. 3.—Nonsecretory endometrium, resembling early interval type, removed on twenty-fourth day of twenty-eight-day cycle.

twenty-ninth day of the cycle showed the endometrium depicted in Fig. 2. It is of a nonsecretory hyperplasia pattern, so that ovulation had obviously not occurred. Another instance of the same type is shown in Fig. 3.

As to the incidence of the anovulatory cases in our own material, I cannot as yet give any accurate figures, though the question is now being studied in our laboratory by Dr. Howard C. Jones. I can only repeat the statement I have made in previous papers, that the anovulatory mechanism is certainly the exceptional one among women in general, but that it is not rare in the small group of sterility cases in which all other factors can apparently be excluded. The microscopic examination of

the premenstrual endometrium in the anovulatory cases will show either a proliferative picture similar to that seen in the interval phase of the usual menstrual cycle, or it will show a greater or lesser degree of hyperplasia, with at times a definite Swiss-cheese pattern.

The technic which we employ in securing tissue for study was recently described in the *Journal of the American Medical Association*, so that it need not be discussed here. Suffice it to say that the aspiration curette-cannula which we have devised, for use with the electric motor suction apparatus, has been highly satisfactory for this purpose, and for many others. It takes only a few moments, almost never requires an anesthetic, causes no great pain, and makes hospitalization unnecessary.

We have extended the use of this technic to various other indications. For example, when adenocarcinoma of the fundus is suspected, aspiration curettage is done without anesthesia, the microscopic examination made at once, and, if malignancy is found, the radical operation proceeded with. In a recent patient, again, one of my colleagues demonstrated tuberculosis of the endometrium, although this had not been suspected. I would again call attention to the rich possibilities of this simple technic in studying the condition of the endometrium in cases of endocrinopathic amenorrhea, for undoubtedly a cycle occurs in some patients even though there is no bleeding phase. Finally, a systematic study by this method, in patients in whom coitus is properly timed in relation to the menstrual periods, is quite sure sooner or later to make embryologists happy by the finding of fertilized eggs at stages much earlier than the Miller ovum, possibly of eggs not yet implanted.

## ENDOCRINE FACTORS IN MENSTRUAL BLEEDING

Only very brief attention need be called to certain new aspects of a problem which is anything but new. I refer to the question of the hormone mechanism of menstrual bleeding. As this has been more fully discussed elsewhere, I shall state simply that the evidence of recent years has seemed to indicate that the responsible factor is a withdrawal or sharp drop in the estrin blood level, thus "knocking the props," as it were, from the endometrium which had been built up under hormonal stimulation. It was rather generally accepted that the catabolic phase thus induced in the endometrium is responsible for its desquamation, with the accompanying bleeding which we call menstruation.

There has always, however, been a minority of investigators who believe that the responsible factor is the withdrawal of the corpus luteum secretion, progestin. The recent work on the chemical kinship of estrin and progestin makes this difference of viewpoint seem less sharp and less important than formerly, but it is of interest to note that two very authoritative investigators, Engle and Smith, have very recently pro-

duced evidence to support the minority view that withdrawal of progestin rather than of estrin is the endocrine factor of prime importance in precipitating the actual bleeding of menstruation. Through the courtesy of Dr. Engle, I have had the opportunity of reading this paper in advance of its publication in the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, and of making use of the conclusions which were reached.

It would appear, however, that the broad concept of menstrual bleeding as a phenomenon due to endocrine withdrawal remains unchanged. Furthermore, the view that the ovarian hormone drop is induced by a reciprocal inhibiting effect upon anterior pituitary function still seems the most tenable, especially as Clauberg and Breipohl have recently shown that the inhibitory changes produced in the pituitary by progestin and demonstrable by histologic study are quite similar to those produced by estrin. Nor is there any new evidence to change our viewpoint as to the mechanism of the purely estrin-induced type of bleeding, exhibited clinically in so-called functional bleeding and in the occasional case of anovulatory menstruation, or, if one prefers the term, "pseudomenstruation."

## SUMMARY

This paper deals with several problems in the field of reproductive physiology, chosen because of their newness and their importance, and because they indicate new trends in this field. The most outstanding advance of the past few years is the recent work on the chemistry of the male and female gonadal hormones (estrin, progestin, androkinin), indicating as it does the close chemical kinship of all three. Furthermore, a similarly close relation has been demonstrated between these hormones and certain well-known chemical substances of the sterol group, as well as the bile acids, certain vitamins, and certain carcinogenic substances. This last named relationship has sent investigators off full cry on a new scent, and it is even possible that the cancer problem may be unlocked with an endocrine key.

While hitherto reproductive physiology has been concerned almost entirely with endocrinology, investigators are beginning to go beyond the endocrine glands in explaining certain cyclical phenomena, and to speak of a sex center located somewhere in the midbrain. Certain cyclical disturbances of menstruation would seem to justify such an assumption and to suggest also a possible participation of the posterior lobe. One of the most interesting phenomena coming under this head is the weight increase and edema seen in many women at menstruation, and in exaggerated form in the so-called generalized edema of menstruation. This type of cyclical water balance disturbance may be seen even in the absence of a bleeding cycle. Its exact mechanism is not known, but its occurrence seems in some way linked up with a change in the globulin-albumin proportions of the blood serum.

Reference is made again to the undoubted possibility that periodic bleeding, clinically interpreted by the patient as normal menstruation, may occur without ovulation. The bearing of this on the study of sterility is obvious, for it undoubtedly explains some cases. The technic which we have found most satisfactory in determining whether or not a patient is ovulating is briefly described.

Finally, brief reference is made to recent investigations suggesting that menstrual bleeding is due to withdrawal of progestin rather than of estrin, as has been generally accepted. Because of the now well-established chemical relation between estrin and progestin, and the fact that they exert a similar inhibiting effect upon the hypophysis, there is no material change in the general concept of the mechanism responsible for the bleeding of menstruation.

## REFERENCES

*Aschheim, S.:* Arch. f. Gynäk. **132:** 179, 1927. *Butenandt, A.:* Deutsche med. Wchnschr. **55:** 2171, 1929; Ztschr. f. physiol. Chem. **208:** 129, 1931; Ibid. **210:** 268, 1932; Zentralbl. f. Gynäk. **59:** 71, 1935. *Doisy, E. A., Veler, E. D., and Thayer, S. A.:* J. Biol. Chem. **86:** 499, 1930. *Marrian, G. F.:* Biochem. J. **24:** 1021, 1931; Physiol Rev. **13:** 185, 1933. *Siebke:* Arch. f. Gynäk. **156:** 317, 1934. *Schoeller, W.:* Deutsche med. Wchnschr. **58:** 1531, 1932; also Lancet **1:** 38, 1933. *Allen, W. M.:* Am. J. Physiol. **92:** 174, 1930. *Fels, K., Slotta, K. H., and Ruschig, H.:* Klin. Wchnschr. **13:** 1207, 1934. *Butenandt, A., Westphal, U., and Hohlweg, W.:* Ztschr. f. physiol. Chem. **227:** 84, 1934. *Zondek, B.:* Lancet **2:** 356, 1934. *Cadiz, R., and Lipschütz, A.:* Arch. f. Gynäk. **153:** 593, 1933. *Witschi, E.:* Sex and the Internal Secretions. Edited by Edgar Allen. Baltimore, 1932, Williams & Wilkins Co., Chapter V. *Novak, E., and Brawner, J. H.:* Am. J. Obst. & Gynec. **28:** 637, 1934. *Dodds, E. C.:* Lancet **1:** 931, 1934. *Murray, W. S.:* J. Cancer Res. **12:** 18, 1928. *Cook, J. W., and Dodds, E. C.:* Nature **131:** 205, 1933. *Overholser, M.D., and Allen, E.:* Surg. Gynec. Obst. **60:** 129, 1935. *Hofbauer, J.:* Zentralbl. f. Gynäk. **54:** 2393, 1930. *Geschickter, C., Lewis, D., and Hartman, C. G.:* Am. J. Cancer **21:** 828, 1934. *Lacassagne, A.:* Compt. rend. Acad. d. sc. **195:** 630, 1932. *Loeb, L.:* J. A. M. A. **104:** 1597, 1935. *Smith, P. E.:* J. A. M. A. **88:** 158, 1927. *Smith, P. E., and MacDowell, E. C.:* Anat. Rec. **46:** 249, 1930. *Sweeney, J. S.:* J. A. M. A. **103:** 234, 1934. *Thomas, W. A.:* J. A. M. A. **101:** 1126, 1933. *Eufinger:* Monatschr. f. Geburtsh. u. Gynäk. **74:** 139, 1926. *Eufinger, H., and Goldner, M.:* Monatschr. f. Geburtsh. u. Gynäk. **73:** 62, 1926. *Eufinger, H., and Spiegler, R.:* Arch. f. Gynäk. **135:** 223, 1928. *Hohlweg and Junkman:* Arch. f. d. ges. Physiol. **232:** 148, 1933. *Kunde, M., d'Amour, C., Carlson, A. J., and Gustavson, R. G.:* Am. J. Physiol. **95:** 630, 1930. *Meyer, R. K., Leonard, S. L., Hisaw, F. L., and Martin, S. J.:* Proc. Soc. Exper. Biol. & Med. **27:** 702, 1930. *Moore, C. R.:* Proc. 2nd Int. Congress Sex Research, p. 293, 1930. *Clauberg, C., and Breipohl, W.:* Klin. Wchnschr. **14:** 119, 1935. *Teel, H. M., and Cushing, H.:* Endokrinologie **6:** 401, 1930. *Philipp, E.:* Zentralbl. f. Gynäk. **54:** 450, 1930. *Corner, G. W.:* J. A. M. A. **89:** 1838, 1927. *Hartman, C. G.:* Anat. Rec. **35:** 13, 1927. *Allen, E.:* Contrib. Embryol. (No. 98). Carnegie Inst., Washington **19:** 1, 1927. *van Herwerden, M.:* Monatschr. f. Geburtsh. u. Gynäk. **24:** 730, 1906. *Novak, E.:* Brit. M. J. **2:** 553, 1933; also Practitioner **132:** 313, 1934. *Tietze, K.:* Arch. f. Gynäk. **156:** 35, 1934. *Mazer, C., and Ziserman, A. J.:* Am. J. Surg. **18:** 332, 1932. *Fluhmann, C. F., and Morse, D. L.:* Am. J. Obst. & Gynec. **21:** 455, 1931. *Adler, K.:* Monatschr. f. Geburtsh. u. Gynäk. **90:** 340, 1932. *Anspach, B. M., and Hoffman, J.:* Am. J. Obst. & Gynec. **28:** 473, 1934. *Novak, E.:* J. A. M. A. **104:** 1497, 1935. *Hartman, C. G., and Novak, E.:* Curtis' Obstetrics & Gynecology, Philadelphia, 1933, W. B. Saunders Co., Chapter IX. *Engle, E. T., and Smith, P. E.:* Am. J. Obst. & Gynec. **29:** 787, 1935. *Clauberg, C., and Breipohl, W.:* Klin. Wchnschr. **14:** 119, 1935. *Engle, E. T., and Smith, P. E.:* Am. J. Obst. & Gynec. **29:** 787, 1935.

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# EXPERIENCES WITH AMNIOTIN IN THE TREATMENT OF GONOCOCCAL VAGINITIS IN CHILDREN*

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THAT the treatment of gonococcal vaginitis with the various chemical disinfectants has, thus far at least, proved to be most unsatisfactory is generally recognized. In our clinic in a series of 50 cases, the average duration of treatment before consistently negative smears were obtained was four months, and the average period of treatment and observation before it was thought safe to discharge the patients was six months. The report of the Bellevue-Yorkville Project,[1] published in 1933, affords ample proof that little progress has been made along the lines of treatment by chemical and vaccination methods. In a series of 212 cases treated with chemicals, vaccines, or a combination of both in the out-patient department, the average duration of "treatment and observation" was fourteen months. Twenty-nine patients were hospitalized and were under "treatment and observation" for an average of 5.3 months. That vaccine is of no value was demonstrated by the fact that a control group which received no treatment improved more promptly than the group receiving vaccine alone. More recently attempts have been made to cure the disease by the use of diathermy. In 1933, R. J. Crossen[2] reported fifteen patients treated by this method. Ten of his cases were classified as acute and required treatment for 21.6 weeks before a consistently negative smear was obtained. In five chronic cases 4.6 weeks were required. Moreover, the practical difficulties in applying this method of treatment to young children are considerable.

In the adult vagina the mucosa is composed of stratified squamous epithelium twenty-five to forty layers deep (Fig. 1, *B*). It is a well-known clinical fact that the adult vagina is resistant to gonococcal infection. In the prepubescent vagina the vaginal mucosa is thin and delicate, composed, as it is, of immature squamous epithelial cells six to fourteen layers deep (Fig. 1, *A*). Its susceptibility to infection by the gonococcus is well known. At puberty the vaginal epithelium undergoes a change to the adult type, and a gonococcal vaginitis existing at this time is observed to subside. Following the work of Allen,[3] who showed that the thin vaginal epithelium of immature animals could be

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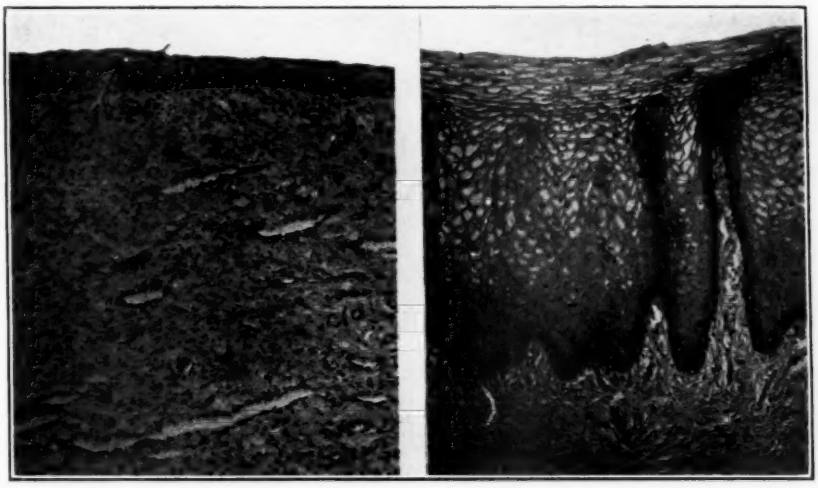
transferred into the adult type by the injection of estrin, it occurred to Lewis[4] that if this change could be produced in the vaginal epithelium of children suffering from vaginitis, a cure was possible. He reported eight cases of gonococcal vaginitis in children treated two or three times daily with 50 units of estrin hypodermically over an average period of twenty-one days. In all these cases the infection cleared. Biopsies from the vagina revealed a definite change in the epithelium from the infantile to the adult type. The infection recurred in two of his cases, one of which was treated again successfully.

We felt that the results of Lewis' small series were sufficiently encouraging to warrant a more complete investigation of the value of the estrogenic hormone in treating this disease. Since March, 1934, we have treated a total of thirty-five patients with the estrogenic preparation,



*A.* *B.*

Fig. 1.—*A*, Normal vagina of a patient fourteen months of age, autopsy. *B*, Normal adult vagina of a patient thirty-seven years of age.

*amniotin*, administered orally, hypodermically, and in vaginal suppositories. We sought to determine:

1. Will the administration of amniotin cure gonococcal vaginitis?

2. If so, by what method of administration and in what dosage is it most effective?

3. What changes may be noted in the genital tract and in the breasts?

4. If changes are noted in these organs, how soon do they appear and when do they disappear after withdrawal of the hormone?

5. Whether or not the administration of the hormone is harmful to the patient.

The cases selected for this study presented clinically typical vulvovaginitis with gram-negative intracellular diplococci in vaginal smears.

Twenty-three of the patients had received no previous treatment. Twelve patients had been treated with vaginal instillations and irrigations without success for periods varying from two weeks to sixteen months. All local treatments were stopped for at least a week before amniotin was begun. The ages ranged from two to eleven years.

A full-time graduate nurse was employed to give the treatments and to aid us in making daily observations. The patients were brought to the dispensary at first three times a week, and later at suitable intervals. Before treatment was begun and upon each subsequent return visit, observations were made on the general health, the breasts, the abdomen, the external genitalia, the presence or absence of vaginal bleeding, and the stained smear. The character of the vaginal washings in normal salt solution was examined microscopically. The internal genitalia were palpated rectally before and after treatment. Clippings were made for microscopic study before treatment and at desired intervals thereafter.

The amniotin was administered orally to six children in daily doses ranging from 400 to 2,000 rat units. The results are given in Table I.

TABLE I. ORAL ADMINISTRATION

| CASE | NO. DAYS TREATED | TOTAL UNITS AMNIOTIN | EPITHELIAL RESPONSE | VAGINAL SMEAR | RESULT |
|---|---|---|---|---|---|
| 7 | 81 | 109,600 | None | Positive | Not cured |
| 11 | 123 | 191,600 | None | Neg. in 116 days | Well |
| 17 | 122 | 168,800 | None | Positive | Not cured |
| 18 | 118 | 185,200 | None | Positive | Not cured |
| 19 | 111 | 180,000 | None | Positive | Not cured |
| 26 | 79 | 158,000 | None | Positive | Not cured |
| Average | 105.7 | 165,533 | None | All pos. except 1 | Not cured 5<br>Well 1 |

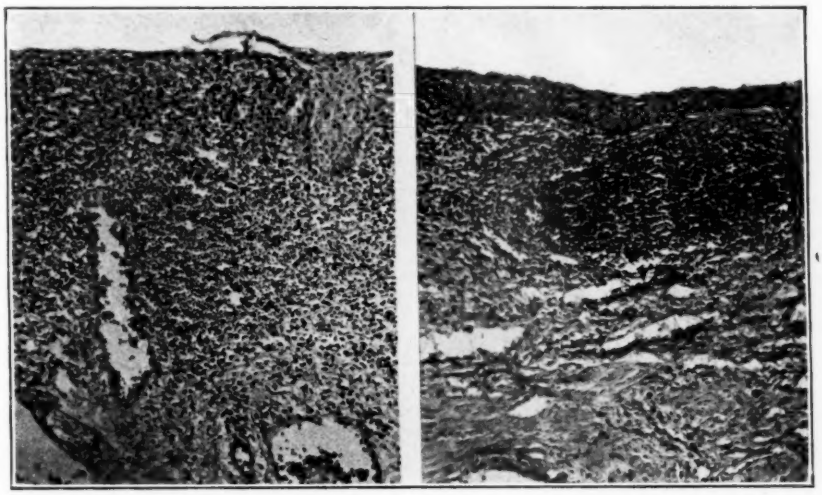
TABLE II. TEN CASES TREATED WITH HYPODERMIC INJECTIONS OF ETHYLENE GLYCOL AMNIOTIN SOLUTION

| CASE | NO. DAYS TREATED | TOTAL UNITS AMNIOTIN | EPITHELIAL RESPONSE | VAGINAL SMEAR | RECURRENCE | RESULT |
|---|---|---|---|---|---|---|
| 1 | 70 | 5,400 | None | Positive | ---- | Not cured |
| 2-a | 31 | 1,550 | None | Neg. after 9 days | After 28 days | Not cured |
| 2-b | 7 | 700 | None | Positive | ---- | Not cured |
| 3 | 19 | 950 | None | Neg. after 5 days | None | Well 1 yr. |
| 4 | 47 | 3,650 | None | Positive | ---- | Not cured |
| 5 | 18 | 900 | None | Positive | ---- | Not cured |
| 6 | 15 | 750 | None | Positive | ---- | Not cured |
| 7 | 11 | 550 | None | Positive | ---- | Not cured |
| 8 | 12 | 600 | None | Positive | ---- | Not cured |
| 9 | 5 | 500 | None | Positive | ---- | Not cured |
| 10 | 4 | 400 | None | Positive | | Not cured |

We found no evidence of activity of amniotin administered orally, as judged by the absence of epithelial change in the vagina. The vaginal

washings showed no desquamation of epithelium and the vaginal biopsies from all these cases showed no change. Fig. 2 shows biopsies from one of these cases (A) before treatment and (B) after the oral administration of 185,000 rat units. It is true that in one case the patient became clinically well and the spreads were negative for gonococci after one hundred and sixteen days of treatment. Nevertheless, in view of the absence of epithelial change found invariably associated with clearing up of the infection after the use of the preparations administered hypodermically and in suppositories, we are inclined to regard this single case as one of spontaneous cure, and conclude that the oral administration in such doses as we have used has no therapeutic value.

A series of ten patients were treated with daily hypodermic injections of amniotin in ethylene glycol solution. Having no preconceived idea



*A.* *B.*

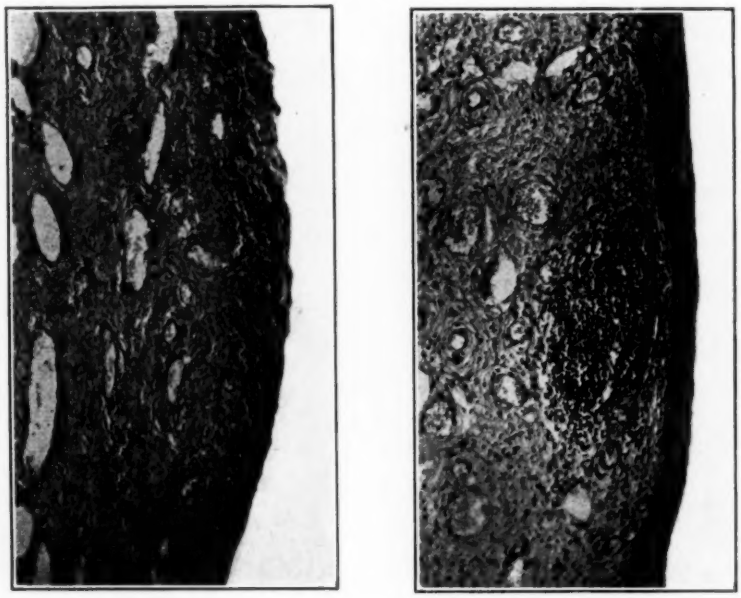
Fig. 2.—*A*, Case 18. Photomircrograph of a section of the vagina of a patient aged eight years. Before treatment. *B*, Case 18, After receiving 185,000 units over a period of one hundred eighteen days.

as to the proper dosage, we started giving 50 rat units daily. When no effect was noted, the dosage was later increased to 100 units per day. The results are given in Table II.

A glance at the chart will show that there was almost universal failure of cure with the amniotin in ethylene glycol solution. Not a single case showed any epithelial change attributable to the injections. Fig. 3 shows the epithelium (A) before, and (B) still immature, after receiving 3,650 units over a period of forty-seven days. In one of the cases the vaginitis cleared up permanently and in another it cleared up but recurred in four weks. In neither of these cases, however, was there any evidence of hormonal action as judged by the vaginal washings or biopsy,

and we do not feel it would be fair to attribute the disappearance of the gonococcus to the hormone. Many of these patients failed to receive an amount of the hormone sufficient to afford a fair trial. The reason for this is the fact that inasmuch as no epithelial response was seen in the early cases, one of which received 5,400 units over a period of seventy days, the preparation in oil was tried. It became apparent almost immediately that the oil preparation showed evidence of much greater activity than the amniotin in ethylene glycol, and the latter, therefore, was discontinued in favor of amniotin in oil.

Having failed in our attempts to produce vaginal epithelial growth with the amniotin in ethylene glycol, we treated a series of patients



*A.* *B.*

**Fig. 3.—Case 4. Photomicrograph of a section of the vagina of a patient aged six years. Before treatment. *B*, Case 4. After E. G. solution hypodermically for forty-seven days, 3,560 units.**

using the hormone in oil. Daily injections were given, hypodermically, in doses ranging from 50 units to 1,000 units in 1 c.c. volume. Whereas the ethylene glycol solution could be given with little discomfort to the patients, many of them complained of pain and persistent soreness following the injection of the oil solution. Obviously the oil was absorbed very slowly. This has caused us to wonder whether this slower absorption of this preparation, by maintaining a more constant level of amniotin in the tissues, might not be responsible for the better therapeutic effect. Table III summarizes our results with thirteen patients who were permanently cured with the oil preparation.

With this preparation an average of 13.5 days was required before the epithelial shedding began. Usually within a few days after the epithelial reaction became manifest in the vaginal washings, the smears became permanently negative, the average being four days after the beginning of epithelial shedding. As the epithelial desquamation begins, the pus in the vaginal washings is gradually replaced by epithelium and usually within a few days the pus has entirely disappeared and the washings consist of pure epithelium. Fig. 4 shows a typical vaginal smear before treatment, and Fig. 5 a smear from the same vagina after the drug had become effective. A biopsy taken at the latter time shows a marked thickening of the epithelium and a complete or almost complete absence of inflammatory cell infiltration (Fig. 6, *B*). Clinically, at this time the reddening of the vulva has largely disappeared, and the discharge may be gradually drying up although in some cases it is as profuse

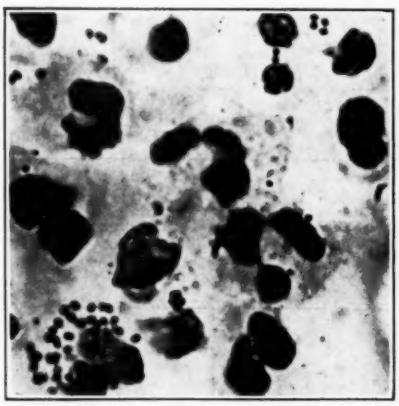


Fig. 4.

Fig. 5.

Fig. 4.—Case 24. Stained vaginal smear before treatment.
Fig. 5.—Case 24. Stained vaginal smear after fifteen days' hypodermic treatment.

as ever. In character, however, this discharge shows a decided change; instead of being purulent it has become thick and curdlike, consisting of desquamated epithelium. After the cessation of treatment this gradually disappears.

As to the optimal daily dosage, we found that the patients given 100 units per day responded as quickly as those given a larger dose. There were five patients treated with the oil preparation hypodermically in which the infection cleared up but recurred as indicated in Table IV.

The recurrences occurred on an average of 22.2 days after the cessation of treatment. Having the benefit of no previous experience, we could determine only by trial and error just how soon the treatment could be stopped after the negative smears were obtained. In the above group we stopped treatment, on an average, five days after the first permanently negative smear. This was obviously too soon and probably accounts for

the recurrences, for in the group of patients who were cured and remained well, treatment was continued twelve days after the first permanently negative smear.

TABLE III. THIRTEEN CASES PERMANENTLY CURED WITH AMNIOTIN IN OIL

| CASE | AGE | NO. DAYS TREATED | TOTAL UNITS AMNIOTIN | DAYS FOR EPITHELIAL RESPONSE | DAYS FOR NEG. SMEAR | DURATION OF CURE TO DATE |
|---|---|---|---|---|---|---|
| 1 | 3 | 24 | 5900 | 15 | 19 | 11 months |
| 2 | 5 | 16 | 1600 | 8 | 12 | 2½ months |
| 4 | 6 | 17 | 1700 | 7 | 7 | 11 months |
| 8 | 4 | 32 | 2900 | 19 | 26 | 11 months |
| 9 | 7 | 34 | 3400 | 9 | 28 | 10 months |
| 10 | 6 | 30 | 3000 | 11 | 22 | 10 months |
| 12 | 4 | 17 | 1700 | 7 | 8 | 9 months |
| 13 | 2 | 16 | 1600 | 7 | 12 | 9 months |
| 14 | 6 | 23 | 7500 | 13 | 19 | 9½ months |
| 16 | 7 | 14 | 1400 | 8 | 8 | 9 months |
| 17 | 4 | 34 | 2900 | 34 | 12 | 4 months |
| 20 | 7 | 33 | 8250 | 11 | 25 | 7½ months |
| 22 | 6 | 37 | 5950 | 26 | 28 | 7 months |
| Average | 5.1 | 25.1 | 3600 | 13.5 | 17.5 | |

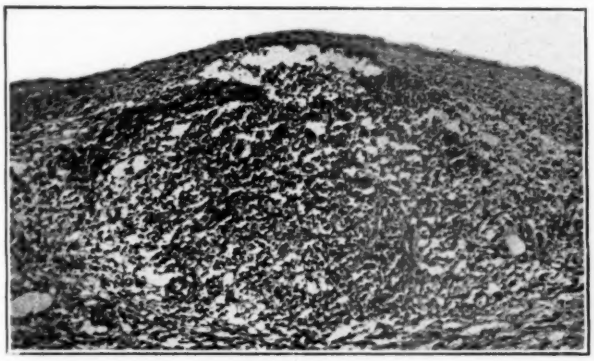
TABLE IV. RECURRENCE AFTER AMNIOTIN IN OIL (5 CASES)

| CASE | AGE | NO. DAYS 1ST TREATMENT | UNITS OF AMNIOTIN | RECURRED AFTER DAYS | NO. DAYS 2ND TREATMENT | UNITS OF AMNIOTIN | DAYS FOR EPITHELIAL RESPONSE | DAYS FOR NEGATIVE SMEAR |
|---|---|---|---|---|---|---|---|---|
| 5 | 3 | 34 | 2750 | 16 | 14 | 1400 | 8 | 10 |
| 6 | 9 | 6 | 300 | 51 | 71 | 16900 | 38 | 68 |
| 15 | 7 | 31 | 3100 | 18 | 22 | 2200 | 6 | 66 |
| 23 | 6 | 36 | 3600 | 7 | 52 | 5200 | None | Pos. |
| 25 | 7 | 66 | 25500 | 21 | Suppository treatment | | | |
| Average | 6.4 | 34.6 | 7050 | 22.2 | | | | |

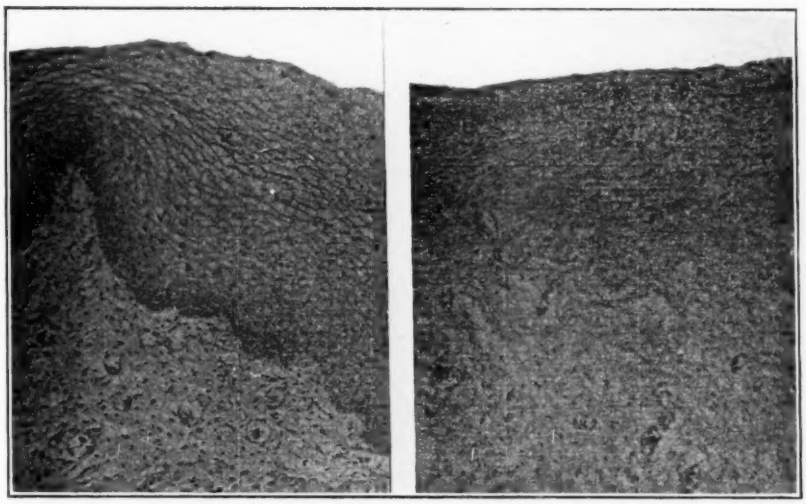
TABLE V. TWELVE CASES PERMANENTLY CURED WITH SUPPOSITORIES

| CASE | AGE | NO. DAYS TREATED | UNITS OF AMNIOTIN IN SUPPOS. | DAYS FOR EPITHELIAL RESPONSE | DAYS FOR NEGATIVE SMEAR | DURATION OF CURE TO DATE |
|---|---|---|---|---|---|---|
| 7 | 10 | 22 | 1,650 | 10 | 10 | 4.5 months |
| 18 | 8 | 18 | 1,350 | 7 | 7 | 4.5 months |
| 19 | 9 | 28 | 2,000 | 14 | 21 | 4.0 months |
| 23 | 6 | 14 | 1,050 | 8 | 8 | 4.0 months |
| 24 | 9 | 15 | 1,125 | 7 | 14 | 4.5 months |
| 26 | 5 | 22 | 1,650 | 10 | 14 | 4.0 months |
| 27 | 10 | 30 | 2,250 | 12 | 23 | 5.0 months |
| 28 | 11 | 23 | 1,725 | 15 | 21 | 4.5 months |
| 31 | 8 | 38 | 2,850 | 25 | 32 | 2.0 months |
| 32 | 7 | 25 | 1,875 | 8 | 15 | 1.5 months |
| 33 | 7 | 22 | 1,650 | 7 | 7 | 2.0 months |
| 35 | 4 | 59 | 4425 | 34 | 41 | 1.0 months |
| Average | 7.8 | 26.3 | 1,967 | 13.1 | 17.8 | |

Among the children treated with the oil preparation there were four who were not cured; these failed to respond to the hormonal action as judged by the vaginal washings and biopsies; yet in some of the cases which failed to respond, an enormous amount of the hormone was used. In one case, 16,800 rat units were injected over sixty-three days, a much more intensive and longer treatment than was required to cure most of the cases with this preparation. The explanation for these refractory



*A.*



*B.* *C.*

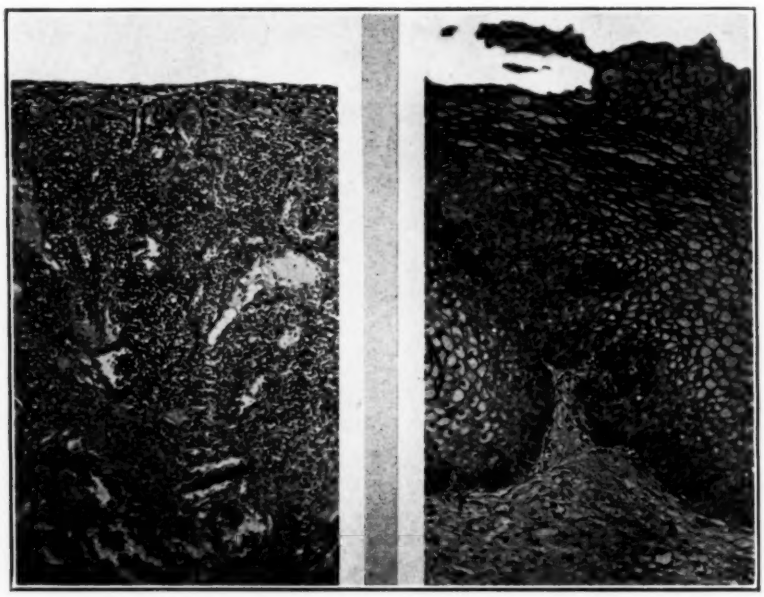
Fig. 6.—*A*, Case 16, before treatment. *B*, Case 16, after ten days, 100 units of oil hypodermically per day, 1,000 units. *C*, Case 16. Four months after cessation of treatment.

cases is not apparent, but it is worthy of note that for the most part the failures occurred in the older children of the group. The average age in the recurrent group was 8.5 years, in contrast to the average age of 5.1 years in the group who were permanently cured with this preparation.

Finally, we tried another method of adapting the estrogenic hormone to the treatment of gonococcal vaginitis. Gelatin suppositories contain-

ing 75 rat units of amniotin were used daily in a series of seventeen cases. Of these, nine had failed to respond to the oral and hypodermic methods, and eight had received no previous treatment. Inasmuch as there is a tendency to loss of a considerable portion of the suppository after melting when the patient is up and about, we recommend that the suppository be used at bedtime. The ease of administration by suppository is obvious. The results are tabulated in Table V.

From Table V it may be seen that an average of 13.1 days was required before the epithelial shedding began, and 17.8 days were required for a consistently negative smear. The average duration of treatment was 26.3 days. It is interesting to note the remarkable similarity of



*A.* *B.*

Fig. 7.—*A*, Case 29, before treatment. *B*, Case 29. Suppositories for twenty-five days, 1,875 units.

these figures with those of the oil hypodermic group in whom the number of days for epithelial shedding was 13.5, for a consistently negative smear 17.5, and for complete treatment 25.1. In other words, the time required for the action of the drug was practically the same whether administered hypodermically or by suppository. The number of units required for this activity, however, was almost twice as great for hypodermic administration as was required per vaginam. It was also our impression that the vaginal epithelial change was more marked when the drug was administered per vaginam (Fig. 7, *A* and *B*). The difference in the effect upon the breast tissue is also worthy of note. Practically all of the patients who received considerable quantities of amniotin hypo-

dermically showed a certain amount of breast hypertrophy, whereas none of the group receiving treatment by suppositories showed any breast change. The facts that less of the hormone was necessary to produce a cure, that the epithelial change was more pronounced, and that there was no breast change when the drug was administered vaginally, have led us to conclude that there is some local action which takes place, due to an increased concentration of the drug in the pelvic tissues.

There were five cases which recurred after suppository treatment which are recorded in Table VI.

TABLE VI. RECURRENCE AFTER SUPPOSITORY TREATMENT (5 CASES)

| CASE | AGE | DAYS TREATED | RECURRED AFTER | DAYS SUBSEQUENTLY TREATED | NO. UNITS AMNIOTIN | DAYS FOR EPITHELIAL CHANGE | NEGATIVE SMEAR | RESULT WELL AFTER |
|---|---|---|---|---|---|---|---|---|
| 21 | 9 | 21 | 4 mo. | 18 | 1,350 | 9 | 9 | 2 weeks |
| 25 | 7 | 20 | 14 days | 59 | 4,425 | 23 | 37 | 2 weeks |
| 29 | 5 | 25 | 10 days | 16 | 1,200 | 8 | 8 | 2½ months |
| 30 | 3 | 33 | 23 days | 21 | 1,575 | 7 | 7 | 4 weeks |
| 34 | 7 | 48 | 8 days | 26 | 1,950 | Persisted | 12 | 2 weeks |
| Aver. | 6.2 | 29.4 | 35 days | 28.0 | 2,100 | 11.8 | 14.6 | 4 weeks |

All of these five patients who had recurrences following the suppository treatment were promptly cured by retreatment with suppositories. It is interesting to note that the length of time required for epithelial change and negative smears was reduced when they were retreated, suggesting that perhaps some amniotin was still retained in the tissues. Inasmuch as the suppository group represents our most recent study, the length of time during which these recurrent cases have been well is necessarily short. The explanation of these recurrences offers certain difficulties, inasmuch as the children were not in an institution, and the question of reinfection must always be considered. In one instance, for example, we feel certain that this was the explanation for the patient who steadfastly denied sexual contact, returned with a primary syphilitic lesion as well as the gonococcal infection. In order not to mask results, we used no accessory treatment with the amniotin. It is possible that the percentage of recurrences may be reduced if irrigations are used in conjunction with the suppositories at the time of the epithelial shedding. Another procedure which may result in a greater percentage of permanent cures and which we intend to carry out in a subsequent series is to attempt to maintain the epithelial thickening over a longer period of time by the use of a suppository once or twice a week after the active treatment has been stopped.

TABLE VII. SUMMARY AND COMPARISON OF METHODS

| METHOD OF TREATMENT | NO. PATIENTS TREATED | NO. PATIENTS WELL | PER CENT WELL | AVERAGE DAYS TREATED | AVERAGE NO. UNITS AMNIOTIN |
|---|---|---|---|---|---|
| Oral | 6 | 1 | 16.6 | 123 | 191,600 |
| Hypodermic E. G. preparation | 10 | 1 | 10.0 | 19 | 950 |
| Hypodermic oil preparation | 22 | 16 | 72.2 | 27 | 4,206 |
| Vaginal suppository | 17 | 17 | 100 | 27 | 2,024 |

The table is self-explanatory and shows clearly the superiority of treatment by the suppository method. At present all of the thirty-five patients treated are well. Those who failed to respond to the oral or ethylene glycol hypodermic administration were subsequently cured by hypodermic oil administrations or vaginal suppositories. Patients who were resistant to the hypodermic oil preparation were promptly cured with suppositories.

One of the first and most essential requisites of any treatment is that it do no harm. During these experiments we were constantly on the lookout for any untoward effects. None were noted except some local reaction about the site of the hypodermic oil administrations. Considerable tender induration could often be felt and in one case a sterile abscess formed. It is our impression that the discomfort during and following the oil injection offers a distinct disadvantage to this method of treatment. There were no cases in the entire series in which there was any evidence of involvement of the upper genital tract. Rectal palpation of the internal pelvic organs showed no gross change. The question of any subsequent ill effect as the result of the hormonal action upon the genital tract must be considered. It was shown by the biopsies that the effect on the vaginal mucosa was very transient. Fig. 6, *C* shows the typical retrogression which had taken place on an average of four weeks after termination of treatment. Inasmuch as the vaginal mucosa is the most sensitive index of the action of the estrogenic hormone, it would seem likely that there remains no permanent effect upon the uterus or ovaries. That this is true is borne out by the work of Allen and Diddle[5] who gave monkeys doses of amniotin comparable to those used in the treatment of vaginitis. Examination of the monkey's ovaries thirty days after the cessation of treatment showed them to be histologically normal. H. B. Shumacher[6] working with mice came to exactly the same conclusions. Hence, judging by all clinical and laboratory criteria, it would appear that there is no evidence that the administration of the hormone is harmful.

## SUMMARY AND CONCLUSIONS

1. Amniotin administered orally or hypodermically in ethylene glycol solution is of no value in the treatment of gonococcal vaginitis. We have been unable to demonstrate any effect of the hormone on the vaginal mucosa or breasts.

2. Amniotin in oil has proved effective both in the production of maturation of the vaginal mucosa and in its therapeutic action in gonococcal vaginitis in 72 per cent of the cases. In most of the patients receiving prolonged treatment breast hypertrophy was noted.

3. Amniotin in suppository form has been proved to be effective in the production of mature vaginal epithelium and in its therapeutic effect in gonococcal vaginitis in all the cases in which we have used it. This group included some cases which had been resistant to the hormone when administered hypodermically in oil.

4. The epithelial change produced by the hormone, whether administered hypodermically or in suppositories, is transient, and there is no clinical or experimental evidence to show that its administration is harmful in dosage necessary to cure this disease.

5. So far as our experience has gone we have concluded that amniotin administered in suppository form is superior to any other known method of treating gonococcal vaginitis.

The authors wish to express their thanks to Dr. Edwards A. Park and the Pediatrics Staff for their cooperation in carrying out this study.

## REFERENCES

(1) Report of a Project of the Bellevue-Yorkville Health Demonstration of New York City, by Walter M. Brunet, M.D., Dora M. Tolle, M.D., Sara Alicia Scudder, Anne Ruth Medcalf. Reprinted from Hospital Social Service Magazine, Supplement No. 1, March, 1933. (2) *Crossen, R. J.:* J. Pediatrics **6**: 82, 1935. (3) *Allen, Edgar:* Sex and Internal Secretions, Baltimore, 1932, Williams and Wilkins Co. (4) *Lewis, R. M.:* Am. J. Obst. & Gynec. **26**: 593, 1933. (5) *Allen, E., and Diddle, A. W.:* Am. J. Obst. & Gynec. **29**: 83, 1935. (6) *Shumacher, H. B.:* Personal communication. *Nabarro, David:* Lancet **228**: 604, 1935. *Miller, J. R.:* Am. J. Obst. & Gynec. **29**: 553, 1935. *Brown, Joseph:* J. A. M. A. **102**: 1293, 1934. *Huberman, J., and Israeloff, H. H.:* Ibid. **103**: 18, 1934.

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**Fournier, R.: An Exceptional Secondary Accident After Spinal Anesthesia for Cesarean Section,** Rev. franç. de gynec. et d'obst. **30**: 148, 1935.

The author reports a case in which after a spinal anesthesia for a cesarean section, a patient developed clonic, generalized convulsions followed by a period of coma. He points out that epileptic convulsions rarely occur after a spinal anesthetic. Forgue and Basset in their report of 1928 mention only two such cases which occurred among 130,000 spinal anesthesias. However, during the discussion of this paper, four other cases were mentioned. The author believes that two factors are involved in the production of convulsions after spinal anesthesia. The first is a disequilibrium in the tension of the cerebrospinal fluid, and the second is toxicity of the substance injected into the spinal canal.

J. P. Greenhill.

# PROTEIN STABILIZATION IN PREECLAMPSIA AND ECLAMPSIA*

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CERTAIN results of investigation of the toxemias of pregnancy, particularly preeclampsia and eclampsia, are presented herewith. The study was conducted at the Elizabeth Steel Magee Hospital from Jan. 7, 1922, to Sept. 1, 1933. During this period there were 24,533 deliveries, of which 139 were eclampties, an incidence of 0.566 per cent. The eclamptic mortality was 21.5 per cent and these deaths constitute 9.36 per cent of the total maternal mortality.

Exercising the viewpoint that the logical solution of the problem lies in prevention rather than attempt at cure after eclampsia has developed, a special effort was made to correlate the clinical and laboratory findings in the hope of adding further to our knowledge of the fundamental factors contributing to the final picture of eclampsia. The plan of investigation included analysis of the history, clinical findings and course, as well as extensive laboratory study. Much of this assembled mass of clinical and laboratory data is in corroboration of previous observation. However, there are certain findings of special significance.

That we may not lose ourselves "in a maze of phantasies, revolving in idle circles," the discussion is presented in three divisions: (1) The changes in the maternal constitution incident to so-called physiologic gestation. (2) The outstanding clinical features of preeclampsia and eclampsia, and notes on treatment with reference to the clinical use of an alcoholic extract of liver known as heparmone. (3) The application of protein stabilization as a measure of study of preeclampsia and eclampsia.

## 1. CHANGES IN THE MATERNAL CONSTITUTION INCIDENT TO SO-CALLED PHYSIOLOGIC GESTATION

The maternal constitution undergoes profound changes in the course of so-called normal pregnancy. Increase in basal metabolic rate has been variously estimated from 4 to 30 per cent.[22] This increase in basal rate is proportional to the combined surface area of mother and fetus. The thyroid gland shows a definite hypertrophy which is a true hyperplasia, and the chromophile cells of the parathyroid bodies increase in number.[22]

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The pituitary gland undergoes hypertrophy in its anterior lobe.[22] There is marked hypertrophy of the cortex of the adrenals.[22] Changes in the islet tissue of the pancreas have not, to our knowledge, been demonstrated. The ovaries show atresia of the follicles with hyperplasia of the inner layer of the theca.[22]

Haden[3] reports 4.2 million and Osgood[13] 4.8 million as the normal red count in the nongravid woman. Galloway[2] reports 3.8 million red cells and 71 per cent hemoglobin in the third trimester of normal pregnancy, which is associated with increase in blood volume according to Kapoth,[22] and a lowered specific gravity according to Lloyd-Jones and Zangemeister.[22] Strauss and Castle[26] have classified the anemias of pregnancy in three groups. The first group shows a progressive increase in anemia through the second trimester, which is followed by an abrupt rise in the third trimester. This group represents the so-called physiologic anemia of pregnancy. The second grouping shows a gestational hypoacidity and is called the hypochromic or chlorotic type. The third group exhibits complete posthistamine gastric anacidity. Strauss and Castle[26] have further shown that the blood picture of infants born of anemic mothers is identical with the blood of infants born of mothers showing no anemia.

Normal pregnancy is characterized by a positive balance of nitrogen, more marked in the latter half of gestation.[4, 6, 10, 11, 14, 20, 21] This positive nitrogen balance is due to the formation of tissue protein in the developing fetus rather than faulty elimination by kidney, since the nonprotein nitrogen of the blood is normal or slightly lowered and the urea fraction definitely below the average found in nonpregnant women. The total protein of the plasma tends to fall, gradually, after the third month, due chiefly to a reduction in the plasma albumin.[22] As a result a relative increase in globulin occurs.

Most observers agree that the level of blood stream sugar approximates normal in uncomplicated pregnancy.[5, 9, 19, 23, 27] There is, however, a frequent variation from the normal in the sugar tolerance curve, and a tendency toward acetonuria which becomes more pronounced when carbohydrates are withheld from the diet.

Gradually increasing from the third month of gestation, the latter part of normal pregnancy is marked by approximately a 30 per cent increase in blood stream fat.[22]

Normal pregnancy is accompanied by a lowering of alveolar $CO_2$ tension, by lowering of $CO_2$ combining power of the blood, and about a 5 per cent reduction in total fixed base. There is a slight lowering of calcium and phosphorus of the blood, decreased sodium concentration of the serum and increased sodium concentration of the corpuscles, while potassium and magnesium remain about the normal levels.[1, 8, 12, 16, 17, 22]

The significance of these changes in the maternal constitution in uncomplicated pregnancy is incompletely understood.

## 2. CLINICAL FEATURES OF PREECLAMPSIA AND ECLAMPSIA

In the analysis of any considerable number of cases of preeclampsia and eclampsia one is increasingly drawn toward the conclusion that a certain type of physical habitus is particularly predisposed to eclampsia,

that the incidence, severity, and mortality in this group rises with the demands of convention on the sensitive, illegitimate mother. In a term of brevity these individuals may be classified as a hypopituitary type with a normal or subnormal thyroid function. The influence of previous acute and chronic infections on the development of such constitutions is a deep but worthy problem. In the past three years no patient with preeclampsia has presented herself at our clinics who has failed to show an intercurrent acute infection, or an active focus of infection. Foci of infection, in the order of importance are: teeth, tonsils, cervix, sinuses, appendix, and gallbladder. Clinical improvement with the eradication of foci of infection has been the rule. Further, close inquiry into the dietary history reveals inadequacies, improprieties, and inabilities in the ingestion, digestion, and assimilation of foods. Strauss and Castle[26] have stressed these factors in relation to the anemias of pregnancy. In gestational toxemias controlled studies constitute a desirable adjuvant.

*Preeclampsia.*—The symptomatic gestational history of the eclamptic, in this series, shows a minimal duration of two weeks and a maximal duration of twenty-eight weeks. The findings in the early gestational toxemias cannot, at present, be utilized to predict the individual who will develop eclampsia. The individual who presents heartburn, scotomas, frontal headache, tinnitus, and formication and numbness of the extremities in the earlier weeks of gestation *often carries severe renal damage*, marked hypertension, and is destined to a premature termination of pregnancy or death.

Weakness and lassitude have been the dominant symptoms from the sixteenth to the twentieth weeks.

Headache appears in 86 per cent of the cases, after the twentieth week of gestation, and is usually frontal or occipital, infrequently bitemporal or sincipital. Transient blindness appears in 20 per cent of the series, and is associated with spasm of retinal vessels, edema of the optic discs, and occasionally with retinitis and retinal detachment. These eyeground changes are referable in but few cases to a known hypertension antedating pregnancy, or an established preexisting nephritis.

Dyspnea is a rather constant finding and is accompanied by precordial distress, positional vertigo, palpitation and anginoid type of pain, a cardiac symptom complex probably referable to the same type of vasospastic change seen in the eyegrounds. Blood pressure shows a tendency to reversal of the normal diurnal rhythm with attainment of the higher levels during the night. A four-hour day and night average of blood pressure, in the antepartum period, is 170/105.5 mm. of Hg with the pulse pressure approximating one and one-half times the normal.

The appetite is variable in 23 per cent of the series, while 68 per cent show nausea and vomiting which may extend throughout the day. There

is a sense of weight in the epigastrium and regional soreness in the right upper quadrant, upon which is superimposed lancinating epigastric pain in 51 per cent of the cases. Pyrosis is usually associated and is worse after the evening meal. Residual gastric content shows lowered or absent free hydrochloric acid and lowering or absence of total acid. Total absence of acid is associated with a history of protracted vomiting or a clinical finding of profound anemia.

The frequency and urgency of a scanty and scalding dysuria require from four to thirty visits to the bathroom each night. The urine, barring alkalies for heartburn and high alkali residue diet, is acid, concentrated, and shows 860 to 38,600 mg. of quantitative protein in twenty-four hours.

Edema gradually becomes generalized and does not disappear with rest.

*Eclampsia.*—In this study one is impressed by the long periods of lavish physical torture which usually exist before the culmination of the tragedy of eclampsia. In more than 60 per cent of the patients, convulsions began between twelve noon and midnight. In the occasional case delivery witnessed the onset of convulsions, while about two-thirds as many convulsions occurred postpartum as the combined antepartum and intrapartum attacks. Of the 139 cases, six cases had a single convulsion. The greatest number of convulsions in one individual was thirty-one.

The preeclamptic symptoms and signs are for the most part accentuated in the eclamptic stage. Elevation of temperature is the rule, in this series reaching 99° to 104°. The skin may assume a peculiar lemon yellow to waxy tint. Cyanosis is usually pronounced and is frequently proportional to the amount of pulmonary edema which, in turn, may be referable to irregularities of rate, rhythm, and force of heart action. The average blood pressure in the eclamptic and intrapartum course is 181/110.1 mm. of Hg with pulse pressure remaining around one and one-half times the normal figure. Blood pressure falls rapidly after delivery, unless renal damage is severe and permanent. In two to twelve hours postpartum, blood pressure begins a secondary rise, which may approach or exceed the maximum pressure in the antepartum period. There is a gradual fall of pressure, over a period of ten to nineteen days, to stabilization around one figure. The average pressure at discharge from the hospital is 127/84.6 with a pulse pressure approximating the normal level.

There may be varying degrees of abdominal distention, rarely pronounced in the earlier stages of eclampsia. Gastric contents invariably contain blood, which probably accounts for the marked increase in the urea fraction of the stomach contents; free hydrochloric acid is usually decreased or absent.

During and immediately after a convulsion the uterus is usually boardlike and remains so from forty seconds to seven minutes. In addition to the uterine tonicity of the convulsive state there may be combined the rhythmic contractions of labor. Frequent convulsions and regular uterine contractions presage fetal death. Intrauterine fetal death is usually accompanied by varying periods of improvement in the clinical condition of the patient.

The urine becomes more concentrated, reddish brown to ashen in color, and decreases in amount, or there may be a total anuria from two to twelve hours. The urinary output varies from 0 to 90 c.c. an hour, the usual output varying from 2 to 30 c.c. an hour. The application of the vasospastic changes seen in the eyegrounds to the severe grades of renal difficulty is supported by the observation of Hinselmann and of Nevermann[22] that 60 per cent of all pregnant women show capillary spasm. Twenty-four-hour quantitative protein shows a variation from 1,945 to 23,219 mg. As the frequency, duration, and severity of convulsions decrease, there is a gradual increase in urine output. In a time interval of five hours, the output may rise from 1 to 2 c.c. an hour to 240 c.c. an hour. The usual improvement in urinary output in the first twelve hours postpartum is followed by a secondary decrease at the end of eighteen to thirty-six hours, which approximates the secondary rise in blood pressure. The urine is now alkaline, of high specific gravity usually, and straw to amber in color. The gradual subsidence in pressure, over ten to nineteen days postpartum, is marked by a gradual improvement in urinary output.

Anemia in preeclampsia and eclampsia is quite common. The average antepartum red cell count in preeclampsia and eclampsia is below the average figure for normal pregnancy and far below the average counts in the nongravid woman. Fifty-six cases of preeclampsia show an average red count of 3.4 million and 22 cases of eclampsia show an average of 3.6 million antepartum. These cases were not associated with hemorrhage or other accidents of labor. Further, the blood picture in the eclamptic is poorly maintained as compared to the preeclamptic. The average postpartum lowering of red cells in 26 cases of eclampsia is three times as great as in 29 cases of preeclampsia. Since faulty and inadequate diets, as well as disturbances in digestion, are factors which have been stressed in relation to the anemias of pregnancy, the quality and quantity of protein administered in preeclampsia assume particular importance.

The results on the chemical analysis of blood alone have largely confirmed the results of others in preeclampsia and eclampsia. The nonprotein nitrogen, on the average, was a little higher than in normal pregnancy, due to varying degrees of renal involvement. However, there is a record of but one patient who presented a blood nonprotein nitrogen in the uremic levels. The blood urea was usually within the

limits of normal for the nonpregnant woman but above the average level of uncomplicated pregnancy. This is consonant with the nonprotein nitrogen findings. Uric acid approximated twice the normal figure. $CO_2$ combining power varied greatly, the limits of variation being 12 and 68, with a tendency for the figure to seek the acid levels. The calcium content of the blood was somewhat lowered, while inorganic phosphorus was distinctly elevated. Fatty acid content of the blood approximated a 50 per cent increase. Sugar, creatinine, chlorides, and cholesterol showed no marked variation from normal pregnancy, while serum proteins occasionally rested in edema levels.

These clinical and laboratory findings, for the most part, were accumulated in a period in which an alcoholic extract of liver, known as heparmone, was being applied in our clinics in preeclampsia and eclampsia. Sixty-seven cases treated with heparmone compared with sixty-six cases treated by various other measures gave the following results in eclampsia:

1. Heparmone had no sustained hypotensive effect antepartum, intrapartum, or postpartum.

2. Heparmone did not control the number, the interval, or duration of convulsive seizures, while its use was frequently accompanied by accentuation of headache, the development of pruritus and generalized subcuticular flushing.

3. Increase in visible edema, in the eclamptic stage, was the rule in the heparmone series.

4. Quantitative urinary proteins were higher in the heparmone series than under any other system of care. However, it is important to state that these results were obtained under a regime of strict enforcement of fluids.

The use of heparmone in the treatment of toxemias of pregnancy has been abandoned in our clinics.

### 3. APPLICATION OF PROTEIN STABILIZATION AS A MEASURE OF STUDY OF PREECLAMPSIA AND ECLAMPSIA

Our summaries emphasize two signal facts in preeclampsia and eclampsia:

1. The evidence of extensive vasospasm is visible in the eyegrounds, demonstrable in blood pressure readings, and is deductable from functional aberrations in brain, in heart, and in kidney.

2. Protein loss may reach surprising magnitudes, even when protein intake lies far below maintenance levels. The severe anemia seen in some of these cases may be referable to inadequate intake of blood-building materials, or to increased destruction of blood. The natural inference in treatment is the attempt to reduce constitutional strain and protect the body from the dissipation of vital protein. Bearing on this disturbance in protein metabolism, the following points are of interest:

1. In the course of normal pregnancy, especially in the latter months, protein should normally be retained to provide for the developing fetus. Therefore, a negative balance, at this time, would be of more serious import.

2. The increased permeability of the kidney to protein dissipation is responsible in part for the reduction of plasma proteins observed in preeclampsia.

3. The higher mortality appears in those cases presenting the greater protein dissipation without adequate replacement.

Extensive investigation of nitrogen balance was instituted in August, 1932. The measures adopted were designed to neutralize protein loss and bring the protein metabolism of the mother into better balance, or a state of stabilization. For purposes of comparison all cases were divided into two classes and placed on a standard regime. The conscious patients, able to cooperate, comprised the first group, while the second group contained those unable to cooperate, i.e., unconscious, or unable to retain food by mouth.

*Group One.*—The total caloric intake was adjusted to the twenty-four-hour resting requirement, using the DuBois chart as a guide. The protein requirement was calculated on the basal requirement, and was also determined from the total nonprotein nitrogen of the urine, plus the urinary protein. For example, if the urine contained 10 gm. of nonprotein nitrogen, this, times the nitrogen factor for protein, 6.25, gave the equivalent amount of protein metabolized, or in the example $6.25 \times 10 = 62.5$ gm. of protein. If the urine, in addition, contained 20 gm. of protein, (ordinarily considered as albumin), this was added to the protein metabolized, giving in the case $62.5 + 20 = 82.5$ gm. of total protein metabolized and lost. The protein intake was adjusted to meet this requirement, the heavier meats being avoided. In addition, a high carbohydrate, low fat diet was employed, the ratio of carbohydrate being four to one of fat. This was adopted because of the well-known sparing action of carbohydrate on protein metabolism, and was an indirect attempt to reduce blood stream fat. Fluid was not restricted below 2,000 c.c. per day. Elimination was secured by the use of milk of magnesia or the daily use of soapsuds enemas. Morphine was used sparingly to control pain or restlessness.

*Group Two.*—These patients were placed on 10 to 25 per cent glucose by vein at four- to six-hour intervals, to the approximate twenty-four-hour caloric requirement. Conscious of the fact that protein dissipation could not be prevented by this measure, nevertheless the glucose supplies readily available energy and tends to minimize the destruction of tissue protein in the patient who is unconscious or unable to retain and assimilate foods by mouth. The lower bowel was emptied by colonic irrigation and a retention catheter, placed in the bladder, was released hourly. These patients were given sufficient morphine to bring the respiratory rate to twelve.

Fifteen referred cases of eclampsia and thirty-one cases of preeclampsia have been studied under this regime. It has not been possible, in this group, to establish nitrogen equilibrium but the nitrogen deficits have been compensated by estimating and feeding the quantitative amounts of protein required. By this simple procedure clinical symptomatology and signs have been much reduced, with the exception of the control of elevations of blood pressure, but the average level of hypertension has been lower. Improvement in anemia has been uniform, the average counts being above the general average of normal pregnancy. Renal function has shown about a 25 per cent increase in efficiency of elimination of fluid, with a distinct rise in urinary nonprotein nitrogen and an increase in the urea fraction of nonprotein nitrogen. The subsidence of hypertension and the return of urinary function to normal postpartum have been more rapid under protein stabilization than had been our previous experience. The eclamptic incidence in our wards has been

reduced to 0.04 per cent. We have had no case, under protein stabilization, develop convulsions, yet the premonitory evidences on admission to the hospital were alarming in all cases studied. Three cases of eclampsia, carrying low blood pressures but with marked symptomatology, have developed in our wards in the period of this study. The symptomatology was unfortunately minimized in the presence of comparatively low blood pressures and efforts in study were not instituted as early as they might have been.

TABLE I. BLOOD CHEMISTRIES. E. M., PREECLAMPSIA, DELIVERED ON 273RD DAY

| | ANTEPARTUM 12 DAYS TEMPERATURE 97.4 | INTRAPARTUM TEMPERATURE 98 | POSTPARTUM 61 DAYS |
|---|---|---|---|
| Nonprotein nitrogen | 20.0 | 26.0 | 27.0 |
| Sugar | 62.0 | 84.0 | 99.0 |
| Urea | 5.2 | 8.5 | 11.1 |
| Uric acid | 2.2 | 3.4 | 3.6 |
| Creatinine | 1.5 | 1.5 | 1.36 |
| Chlorides | 450.0 | 472.0 | 445.0 |
| $C O_2$ | 32.64 | 46.7 | 48.2 |
| Calcium | 9.8 | 10.15 | 9.7 |
| Phosphorus | 2.5 | 3.2 | 2.78 |
| Serum albumin | 4.2 | 4.0 | 3.79 |
| Serum globulin | 2.4 | 1.9 | 1.04 |
| Fat | 432.0 | 456.0 | 421.0 |
| Cholesterol | 132.0 | 205.0 | 225.0 |

*Blood Counts*

| | ANTEPARTUM 15 DAYS | POSTPARTUM 13 DAYS |
|---|---|---|
| R. B. C. | 4,000,000 | 3,860,000 |
| W. B. C. | 11,100 | 12,800 |
| Hemoglobin | 74% | 71% |
| Polymorphonuclears | 88% | 84% |

*Urine Chemistries*

12 DAYS ANTEPARTUM TEMPERATURE $99\frac{1}{5}$

Total nitrogen 6.07 = 37.9375 gm. protein
Nonprotein nitrogen 3.89 = 24.3125 gm. protein

64% of total nitrogen = Nonprotein nitrogen
29% of nonprotein nitrogen = Urea
Protein loss = 13.625 gm.

1 DAY ANTEPARTUM TEMPERATURE 98

Total nitrogen 6.0 = 37.5 gm. protein
Nonprotein nitrogen 5.34 = 33.375 gm. protein

89% of total nitrogen = Nonprotein nitrogen
58% of nonprotein nitrogen = Urea
Protein loss = 4.12 gm.

Our experience in this limited number of cases encourages a report on these results with the hope that others may find this method of approach useful in the study of preeclampsia and eclampsia. The most profound clinical alterations demonstrable in preeclampsia and eclampsia are in the field of protein metabolism: that this has a direct ap-

TABLE II. BLOOD CHEMISTRIES. ANTEPARTUM. E. S., ECLAMPSIA. NOT DELIVERED. INFANT LIVING. PATIENT SYMPTOMATICALLY FREE

| | 202ND DAY OF GESTATION TEMPERATURE 98.3 | 204TH DAY OF GESTATION TEMPERATURE 98.3 |
|---|---|---|
| Nonprotein nitrogen | 28.6 | 33.7 |
| Sugar | 115.0 | 78.0 |
| Urea | 14.3 | 13.8 |
| Uric acid | 4.2 | 4.0 |
| Creatinine | 1.33 | 1.37 |
| Chlorides | 514.0 | 459.0 |
| C $O_2$ | 19.71 | 52.7 |
| Calcium | 12.2 | 9.8 |
| Phosphorus | 2.8 | 2.78 |
| Serum albumin | 3.1 | 2.89 |
| Serum globulin | 2.0 | 1.12 |
| Fat | 580.0 | 500.0 |
| Cholesterol | 135.0 | 100.0 |
| Icterus index | 9.0 | |

*Blood Count*

| | 202ND DAY OF GESTATION |
|---|---|
| R. B. C. | 4,000,000 |
| W. B. C. | 10,600 |
| Hg | 81% |
| Polymorphonuclears | 86% |
| Lymphocytes | 14% |

*Urine Chemistries*

202ND DAY OF GESTATION TEMPERATURE 98⅗

Total nitrogen 10.49 = 65.25 gm. protein
Nonprotein nitrogen 6.25 = 39.06 gm. protein

65.25% of total nitrogen = Nonprotein nitrogen
42.00% of nonprotein nitrogen = Urea
Protein loss = 26.1875 gm.

209TH DAY OF GESTATION TEMPERATURE 98⅗

Total nitrogen 9.47 = 59.1875 gm. protein
Nonprotein nitrogen 5.64 = 35.2500 gm. protein

59% of total nitrogen = Nonprotein nitrogen
77% of nonprotein nitrogen = Urea
Protein loss = 13.9375 gm.

224TH DAY OF GESTATION TEMPERATURE 98⅗

Total nitrogen 4.24 = 26.500 gm. protein
Nonprotein nitrogen 3.82 = 23.875 gm. protein

90% of total nitrogen = Nonprotein nitrogen
83% of nonprotein nitrogen = Urea
Protein loss = 2.625 gm.

plication in the final outcome is more than probable. Any plan of prevention and treatment must take into consideration such measures as will tend to maintain the protein of the mother within the limits of normal pregnancy. Our findings have been such in this study that we propose to direct our efforts along this line in a further investigation of preeclampsia and eclampsia.

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REFERENCES

(1) *Denis, W., and King, E. L.:* Am. J. Obst. & Gynec. **7:** 253, 1924. (2) *Galloway, C. E.:* Am. J. Obst. & Gynec. **1:** 84, 1929. (3) *Haden, R. L.:* Arch. Int. Med. **31:** 766, 1923. (4) *Harding, V. J., Allin, K. D., and Van Wyck, H. B.:* J. Obst. & Gynec. Brit. Emp. **31:** 595, 1924. (5) *Hellmuth, K.:* Klin. Wchnschr. **1:** 1152, 1922. (6) *Hellmuth, K.:* Arch. f. Gynäk. **118:** 18, 1923. (7) *Hermann, E., and Neumann, J.:* Biochem. J. **43:** 47, 1912. (8) *Krebs, O. S. and Briggs, A. P.:* Am. J. Obst. & Gynec. **5:** 67, 1923. (9) *Krebs, O. S., and Briggs, A. P.:* Hospitalstid., Copenhagen **68:** 1039, 1925. (10) *Martin, C. H., and Robison, R.:* Biochem. J. **16:** 407 1922. (11) *McEllroy, W. S., and Pollock, H. O.:* J. Biol. Chem. **46:** 475, 1921. (12) *Oard, H. C., and Peters, J. P.:* J. Biol. Chem. **81:** 9, 1929. (13) *Osgood, E. E., and Haskins, H. D.:* Arch. Int. Med. **39:** 643, 1927. (14) *Peters, J. P., and Van Slyke, D. D.:* Quantitative Clinical Chemistry. Interpretations, Baltimore, 1932, Williams and Wilkins Co., pp. 267 and 268. (15) *Peters, J. P., and Van Slyke, D. D.:* Quantitative Clinical Chemistry. Interpretations, Baltimore, 1932, Williams and Wilkins Co., p. 336. (16) *Plass, E. D., and Bogert, L. J.:* Bull. Johns Hopkins Hosp. **35:** 361, 1924. (17) *Plass, E. D., and Matthew, C. W.:* Am. J. Obst. & Gynec. **12:** 346, 1926. (18) *Pribram, E. E.:* Arch. f. Gynäk. **119:** 57 1923. (19) *Sansum, W. D., and Woodyatt, R. T.:* J. Biol. Chem. **30:** 155, 1917. (20) *Sherman, H. C.:* J. Biol. Chem. **41:** 97, 1920. (21) *Smith, M.:* J. Biol. Chem. **68:** 15, 1926. (22) *Stander, H. J.:* Monographs in Gynecology and Obstetrics by Karl Henry Davis, Hagerstown, Maryland, W. F. Pryor, 1934 **1:** chap. 8. (23) *Stander, H. J., Duncan, E. E., and Sisson, W. E.:* Bull. Johns Hopkins Hosp. **36:** 411, 1925. (24) *Stander, H. J., Eastman, N. J., Harrison, E. P. H., Jr., and Cadden, J. F.:* J. Biol. Chem. **85:** 233, 1929. (25) *Stander, H. J., and Radelet, A. H.:* Bull. Johns Hopkins Hosp. **38:** 423, 1926. (26) *Strauss, M. B., and Castle, W. B.:* Am. J. M. Sc. **185:** 539, 1933. (27) *Tisdall, F. F., Drake, T. G. H., and Brown, A.:* Am. J. Dis. Child. **32:** 854, 1926. (28) *Van Slyke, D. D., Stillman, E., Moeller, E., Ehrich, W., McIntosh, J. F., Leiter, L., MacKay, E. M., Hannon, R. R., Moore, N. S., and Johnson, C.:* Medicine **9:** 257, 1930. (29) *Widdows, S. T.:* Biochem. J. **17:** 34, 1923. (30) *Williams, J. L.:* J. A. M. A. **76:** 1297, 1912. (31) *Zangemeister, W.:* Ztschr. f. Geburtsh. u. Gynäk. **99:** 92, 1903.

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**David-Chaussé, R.: Pruritus Vulvae. Etiologic and Therapeutic Consideration,** Rev. franç. de gynéc et d'obst. **29:** 1014 1934.

For the treatment of pruritus vulvae the author varies medication depending upon the etiology of the condition. For itching due to mycosis he prescribes a special preparation and he lists other drugs for pruritus due to microbic infection, diabetes and other causes. In cases where the etiology is unknown he applies symptomatic treatment. He has not employed radium therapy but believes that x-ray treatments in small doses are often helpful. He has tried the epidural injection route of autohemotherapy and autoserotherapy without any success. On the other hand, the intravenous injection of bromides has given relief. The injection of physiologic serum has not given constant results. Endocrine therapy has produced no favorable effects. For severe cases which resist all treatment surgical intervention is necessary. The various forms proposed are vulvectomy, resection of the presacral nerve, periarterial sympathectomy and bilateral chordotomy. The author believes that in most intractable cases of pruritus vulvae we should search for cellulitis of the pelvis.

J. P. Greenhill.

# THE TREATMENT OF DYSMENORRHEA BY PRESACRAL SYMPATHECTOMY

FLOYD E. KEENE, M.D., PHILADELPHIA, PA.

TEN years ago, Cotte suggested presacral sympathectomy for the relief of pelvic pain, the chief indication being dysmenorrhea. Since then, he has contributed extensively to the subject and numerous publications from other clinics have accumulated in foreign literature, duplicating the excellent results which Cotte has reported. In striking contrast is the paucity of contributions by surgeons in this country. The results of this procedure in the treatment of dysmenorrhea have been reported by Adson and Masson, Counsellor and Craig, DeCourcy, and Wetherell; its value in relieving pain associated with pelvic cancer has been discussed by Behney, and Greenhill and Schmitz. Although the number of patients so treated by each author is small, there is a unanimity of opinion that excision of the presacral nerve is a valuable addition to our therapeutic armamentarium, in that it often affords relief when other methods have failed.

For obvious reasons, presacral sympathectomy for dysmenorrhea is limited in its field of usefulness to young women, hence its value must be judged not only in terms of relieving pain but also by its effects on menstruation and pregnancy. Further, this operation severs the chief sympathetic nerve supply to the bladder and rectum as well as the uterus, and a satisfactory result must include unimpaired function of these organs. The purpose of this paper is to discuss the function of the presacral nerve so far as it bears upon these facts, to review briefly the anatomy necessary to the execution of presacral resection, and to report the results of this operation in seven cases of dysmenorrhea.

## AUTONOMIC NERVE SUPPLY OF THE PELVIC ORGANS

The nervous mechanism which regulates visceral function and other involuntary activities of the body has been designated by Langley as the autonomic nervous system. Composing this system are two groups of nerves, the sympathetic and the parasympathetic, which are antagonistic in their action and whose delicately adjusted coordination or balance is reflected in the normal function of the organs they supply.

The presacral nerve is that segment of the abdominal sympathetic system which extends from the bifurcation of the aorta to the sacral promontory. The term "presacral" which was chosen by Laterjet is anatomically incorrect, since the position is prelumbar and the conforma-

tion is usually that of a plexus rather than a true nerve. More appropriate is superior hypogastric plexus (Hovelacque) or prelumbar plexus (Elaut). This nerve is formed by the union of three roots. The lateral roots are composed of branches from the first and second lumbar ganglia and fibers which have taken their origin from ganglia in the region of the renal arteries. These nerve bundles pass downward to unite with the middle root which is a continuation of the intermesenteric plexus. Thus formed, the nerve is joined by fibers from the third and fourth lumbar ganglia on each side and after crossing the promontory of the

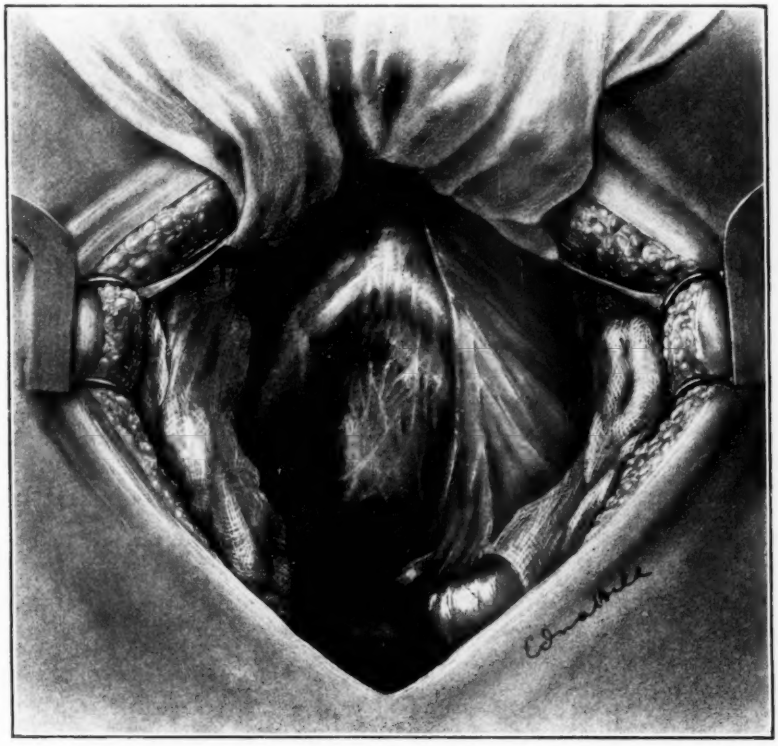

Fig. 1.—Interiliac space exposed. Note inferior mesenteric artery on the left. Presacral and inferior hypogastric nerves not usually visible through peritoneum but are depicted here to show relations of the nerve as well as its usual plexiform arrangement.

sacrum, it divides into the right and left hypogastric nerves. These nerves course along the posterior pelvic wall supplying branches to the ureters and enter the lateral rectal space, terminating in the inferior hypogastric ganglia. Here they are joined by the parasympathetics through the pelvic nerves (nervi erigentes) which are branches of the second, third, and fourth sacral nerves. Emerging from the ganglia, the combined fibers form a plexus anterior to the rectum in the region of the uterosacral ligaments and continue along the internal iliac artery and its branches to supply the genital organs, including the vagina, the

bladder, and the lower portion of the rectum. The sympathetic and parasympathetic nerves contain both efferent and afferent fibers, the latter reaching the spinal cord by way of a detour to the posterior roots.

The main sympathetic nerve supply of the ovary arises in the ovarian plexus and passes downward with the ovarian vessels to the infundibulopelvic ligament where it divides into two branches, one entering the ovary and the other the fallopian tube. A few fibers from the tubal division pass directly to the uterus and others anastomose with the plexus in the broad ligament.

*Anatomic Relations of the Presacral Nerve.*—The presacral nerve lies in what is called by Elaut the interiliac space which is in the form of a triangle with the bifurcation of the aorta as its tip, the common iliac arteries its lateral boundaries, and its base a line across the promontory of the sacrum. On the left side of this space is the inferior mesenteric artery coursing through the base of the mesocolon. Ordinarily this can be displaced to the left, but the root of the mesocolon may extend across the median line of the triangle, making access to the nerve not only difficult but also hazardous. Covering the interiliac space is the posterior parietal peritoneum through which, in thin subjects, the fibers of the nerves may be seen. Immediately beneath the peritoneum, or separated from it by more or less fat, is a sheet of fibrous tissue in which lies the presacral nerve usually in the form of a plexus rather than a single nerve. The plexus in its sheath crosses but is easily separated from the left common iliac vein which is seen as a broad band filling in the upper portion and left side of the triangle. As the nerve approaches the base of the triangle, it lies on the median sacral vessels and the prevertebral fascia covering the last intervertebral disc and fifth lumbar vertebra.

*Function of the Presacral Nerve.*—According to Gask and Ross, our understanding of the human sympathetic nervous system is very imperfect, for clinical experience not only reveals gaps in our knowledge but also casts doubt upon many current beliefs. One is forcibly impressed with the truth of this statement in reviewing the literature dealing with the physiology of the pelvic autonomic nervous system, since an array of conflicting opinions is encountered which warrants the conclusion of Davis that the indication for excision of the presacral nerve must necessarily rest upon a very insecure foundation. However, this foundation becomes more secure when it is realized that many of the opinions expressed are based upon animal experimentation and that with the advent of surgery during the past decade, our knowledge has been enhanced by clinical investigation and observation. Opinions may differ as to the influence exerted by the presacral nerve on a given organ, but we do possess a fairly accurate idea of the effect resection of the nerve will have upon the functional activity of that organ, which is of prime importance to the clinician and pertinent to the subject under discussion. To this end we shall summarize the opinions expressed in a few of the more recent contributions.

*Transmission of the Pain Impulses.*—Gask and Ross state that most if not all of the afferent fibers from the uterus travel in the sympathetic nerves to the spinal cord. According to Fontaine and Hermann, the hypogastric plexus carry the important pathways of sensation from the internal genital organs to the medullary centers. Similar evidence is found in the contributions of Kuntz, Cotte, Leriche, and Learmonth. Adson and Masson agree that presacral fibers undoubtedly carry sensations of pain but in their opinion, the relief of pain in functional dysmenorrhea is obtained not only by cutting the pain fibers but also from interruption of efferent fibers which supply the blood vessels in the genitalia and musculature of the uterus. Davis states that the relief of pain which follows resection of the presacral nerve is probably the result of vasomotor rather than any sensory function, but the absence of sensory fibers is by no means certain. There can be no doubt as to the efficacy of presacral nerve excision in relieving pain in the organs supplied by it, and what appears as incontrovertible evidence warrants the conclusion that the relief is in large measure ascribable to the division of sensory pathways, vasomotor changes being only secondary factors.

*Control of Uterine Function.*—The part played by the sympathetic and parasympathetic nerves in regulating the motor function of the uterus is unknown. To the conflicting opinions regarding the motor and inhibitory influence of these nerves is added evidence that uterine contraction occurs in the absence of nerve stimulation. In proof of this, is the frequently quoted experiment of Rein which shows that spontaneous birth of young in rabbits occurs after section of all extrinsic nerves of the uterus. Cotte refers to the demonstration of Calliburce, who extirpated the uterus from an animal in labor, suspended it in Locke's solution, and observed that contractions continued until fetal expulsion was completed. Of greater value is the clinical evidence pertaining to the regulation of uterine motor function by the nervous system. As to the parasympathetic influence, Fontaine and Hermann cite the observations of Mueller, Brachet, and Gertsmann who have found that neither the section nor the complete destruction of the sacral part of the spinal cord will prevent childbirth, and Kuntz states that under these circumstances, parturition proceeds with abnormal rapidity. Of vital importance to the subject under discussion is the effect of sympathetic ablation upon subsequent pregnancy. Cotte states that in thirty pregnancies after presacral excision he has never observed any evidence of altered uterine contractility. He also reports two patients who were subjected to this operation during the early months of pregancy on account of severe uterine pain. In both, the pain was relieved, pregnancy was uninterrupted, and they were delivered normally at term. Precipitate delivery in a nullipara forty-two years of age is reported by Davis who suggests that it provides some support of the view that the

presacral nerve is an inhibitor and the parasympathetic an excitor of uterine contraction. The only case of full-term pregnancy after presacral excision reported in this country is that of Wetherell. This patient was a nullipara who became pregnant a year and a half after operation. The first stage of labor lasted eighteen hours, the second stage four hours, and delivery was by midforceps because of posterior position of the occiput. The pains were irregular and weak, being in the nature of a backache with no pain in front. Her puerperium was uneventful. Although the exact control of the motility of the uterus is unknown, the concensus of opinion is that presacral sympathectomy does not interfere with parturition.

Ovarian function and the response of the uterus to this function are not directly subject to nervous regulation; the part played by the pelvic nervous system in menstruation has to do in large measure, if not entirely, with its influence on the blood vessels of the genital organs. Resection of the presacral nerve does not alter the normal rhythm of menstruation, but bleeding a few days after the operation and increase in the quantity and duration of the menstrual flow may result from removal of the constrictor influence exerted by the sympathetics upon the blood vessels of the uterus and broad ligaments.

*Control of Bladder Function.*—My remarks on the nervous mechanism concerned in the control of the bladder function are based upon the clinical investigations of Learmonth, who has made valuable contributions to the subject during recent years. Entering into this mechanism are three pathways, the sympathetic, the parasympathetic, and the pudic nerves. The sympathetics (presacral nerves) are inhibitory to the detrusor muscles and motor to the internal sphincter, trigone, and the ureteral orifices; they also exert a constrictor influence upon the blood vessels of the bladder. The parasympathetics (pelvic nerves) are motor to the detrusor muscles and inhibitory to the internal sphincter. The pudic nerves supply motor fibers to the compressor urethrae muscle and sensory fibers to the posterior urethra and internal sphincter. Normal micturition is dependent upon the integrity of the parasympathetic pathways which are unaffected by division of the presacral nerve. However, this nerve does stimulate sphincteric contraction and Learmonth's cystoscopic studies show that immediately after presacral excision, the sphincter, trigone, and ureteral orifices are relaxed. Within three weeks, this relaxation has disappeared, and he believes that the ability of the sphincter to remain closed after ablation of the motor influence is due to an inherent tonus which normally is merely reinforced by the sympathetic supply. Also of importance in its bearing upon presacral sympathectomy is the transmission of sensory impulses from the bladder. The sensation of fullness which is translated into a desire to urinate is transmitted by the afferent fibers of the parasympathetic (pelvic)

nerves; also along this pathway travel thermal and tactile impulses. Painful sensations due to an overdistended bladder or disease are transmitted by way of the sympathetic (presacral) nerves.

Clinical application of these facts is found in the use of presacral sympathectomy in the treatment of cord bladder as suggested by Learmonth and Braasch, of neurogenic dilatation of the ureters and of certain types of vesical pain. They also explain the absence of bladder impairment after excision of the presacral nerve.

*Control of Rectal Function.*—The sympathetic nerves which are blocked by presacral excision supply the lower rectum and the internal sphincter of the anus, the external sphincter, which is composed of voluntary muscle, being supplied by the inferior hemorrhoidal branches of the pudic nerves. The influence of the sympathetic and parasympathetic nerves on the rectum as well as the internal sphincter is similar to that exerted on the bladder, the one being inhibitory to the musculature of the rectal wall, and motor to the sphincter, the other exerting opposite effects. The ability of the internal sphincter to remain closed after section of its motor nerve supply may be explained in the same manner as Learmonth has applied to the vesical sphincter. As a further safeguard against incontinence is the external sphincter with its separate nerve supply. Further, as Kuntz states, both sphincters are normally in tonus, the force of tonic contraction of the external sphincter being greater than that of the internal. An abundance of clinical evidence shows that excision of the presacral nerve does not impair rectal function, in fact obstinate constipation may be relieved by it.

*Selection of Cases.*—The type of functional dysmenorrhea which responds most favorably to presacral excision is that in which the pain is located in regions corresponding to the final distribution of the presacral nerve. To this type, Cotte has applied the term hypogastric plexalgia in the belief that the pain is due to a dysfunction or actual disease of the nerves which compose the plexus. The spasmodic pain comes on a few days before or with the onset of the flow, and its point of maximum intensity is in the uterus, radiating to the sacrum or coccyx and often accompanied by bladder irritability. Cotte emphasizes the importance of differentiating this type of dysmenorrhea from that indicating involvement of the ovarian sympathetic plexus in which the pain is located in one or both sides of the pelvis, radiating to the lumbar region. Under these circumstances, the prognosis of relief from presacral sympathectomy is less favorable. For this type of pain, denervation of the ovaries by excision of the nerves in the infundibulopelvic ligament or by section of the ligament has been suggested; the former procedure would seem to present insuperable technical difficulties, and interference with the ovarian blood supply is a formidable objection to the latter.

Cotte presents convincing evidence to prove the value of presacral sympathectomy as a supplementary procedure to operations on the pelvic organs for organic lesions which may contribute to the dysmenorrhea. In a series of 200 cases, correction of the pelvic defects with presacral nerve excision gave a greater incidence of relief than in a similar group in which excision of the nerve was omitted.

*Technic of Operation.*—Through a lower midline incision extending to the umbilicus, the field of operation is exposed by packing the small intestines upward and to the right and retracting the sigmoid to the

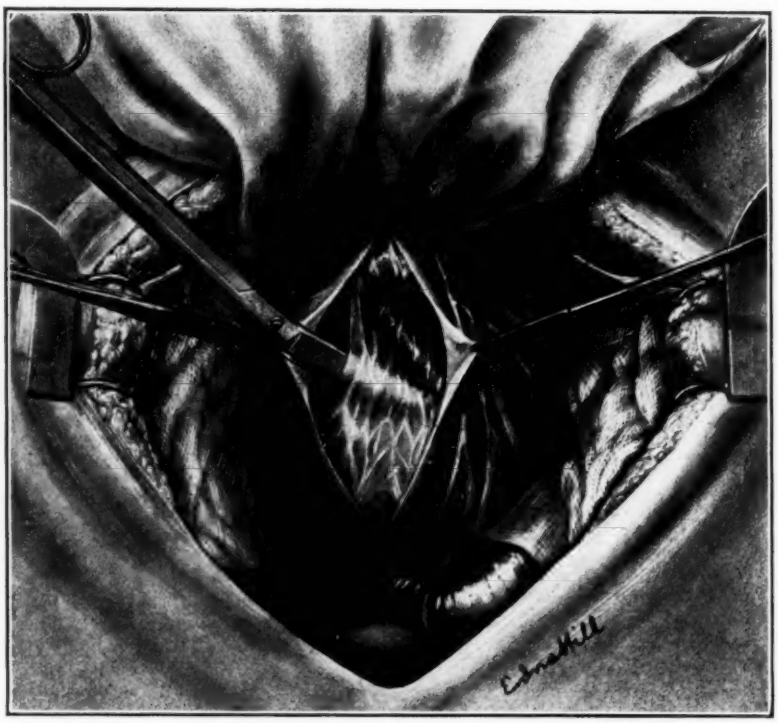

Fig. 2.—Beginning resection of fibrous sheath and nerve over right common iliac artery.

left. The landmarks thus exposed are the bifurcation of the aorta, the common iliac arteries, and the promontory of the sacrum. On the left side of this space is the inferior mesenteric artery coursing through the base of the mesocolon. The root of the mesocolon may extend across the interiliac space, overlying the presacral nerve. Under these circumstances, the peritoneal incision is made well to the right of the midline and exposure of the nerve beneath the thick, vascular mass is a difficult as well as hazardous procedure. Ordinarily, the posterior parietal peritoneum is incised in the midline just above the sacral promontory, and the incision is continued upward to the bifurcation of the aorta and downward over the promontory. The flaps of peritoneum are elevated

by blunt dissection as far as the common iliac arteries, exposing a sheet of fibrous tissue covered by more or less fat. This sheet of tissue contains the fibers of the presacral nerve. In thin subjects, the fibers can be seen and felt, but a thick layer of subperitoneal fat complicates the situation, making recognition and excision of the nerves more difficult. The separation of the sheath and nerve is made en masse, beginning over the right common iliac artery near the bifurcation of the aorta. By gentle blunt dissection, the separation is continued over the left iliac vein to the left common iliac artery. As Cotte states, the tissue surrounding the nerves in this area is very delicate, and its tensile strength is supplied by the nerve fibers which it contains. The sheet of tissue

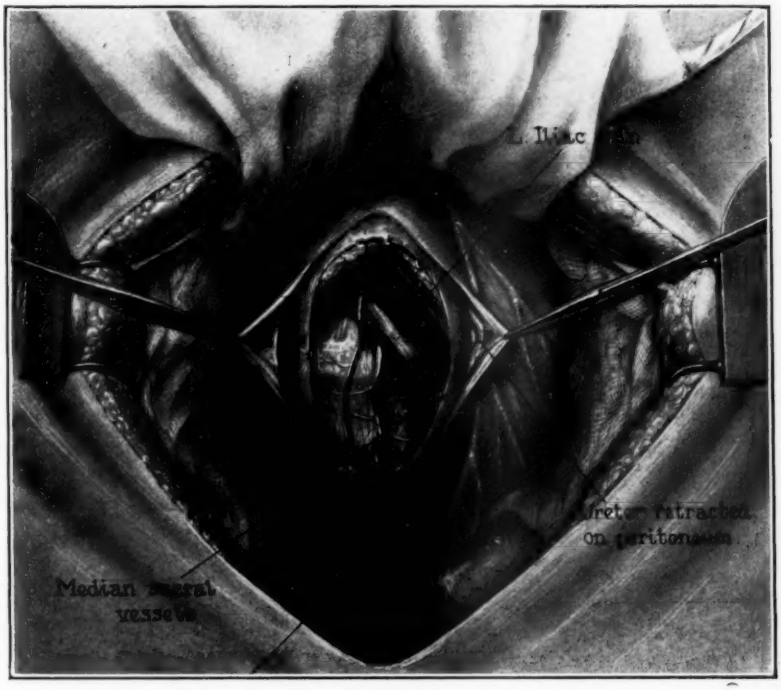

Fig. 3.—Operation completed, showing extent of resection and structures occupying interiliac triangle.

thus liberated is elevated and the dissection is carried downward, avoiding the median sacral vessels, until the division into the hypogastric nerves is recognized. The upper and lower attachments are severed after ligation with fine, plain catgut to avoid troublesome oozing from the vasa nervorum and the incision in the posterior parietal peritoneum is closed with a continuous suture.

*Report of Cases.**—This report summarizes the results of presacral sympathectomy in seven cases of severe, intractable dysmenorrhea. In

*My associate, Dr. Charles A. Behney, was among the first in this country to employ presacral sympathectomy for the relief of pelvic pain, and my adoption of the procedure is due in large measure to his influence. For his valuable assistance, I am deeply indebted.

five, the dysmenorrhea was of the functional type, the pelvic organs being normal with the exception of one who had been subjected to a left salpingo-oophorectomy. Extensive endometrial transplants in the culdesac and on the posterior surface of the broad ligament were present in one patient, and in another, the small, acutely anteflexed uterus was retrocessed. In this last patient, the uterus was suspended and the appendix removed; in the remainder, presacral sympathectomy was the only operation performed.

With the exception of dribbling of urine in one patient for a few days after operation, the immediate convalescence differed in no respect from that of the ordinary laparotomy. As to the remote results, the menstrual rhythm has shown no alteration. In one the quantity and duration of the flow have increased slightly, and in another there has been a diminution. In none has there been impairment of bladder or rectal function. The results as regards relief of pain are summarized as follows:

CASE 1.—Patient aged twenty-four years, married, nullipara, operation Feb. 15, 1934. Pelvic organs normal. Before operation, the patient had pelvic discomfort with attacks of severe colicky pain for eighteen days prior to and during the periods. Now pain is present only during the period and is just as severe as before operation.

CASE 2.—Patient aged twenty-three years, married, nullipara, operation May 17, 1934. The patient had extensive endometrial transplants in the culdesac and on the posterior surface of the broad ligaments. The uterus was retroverted and the ovaries were normal. The extent of involvement and the history of great increase in severity of the dysmenorrhea during the year preceding the operation leave no doubt as to the part played by the lesion in the production of pain. The pain has been entirely relieved by presacral sympathectomy.

CASE 3.—Patient aged twenty years, single, operation June 29, 1934. Pelvic organs normal. No relief from dilatation of the cervix and Baldwin drain. Since presacral excision, only slight discomfort during the first few hours of the period.

CASE 4.—Patient aged thirty-two years, married, nullipara, operation Sept. 18, 1934. Uterus small, acutely anteflexed, and retrocessed. Ovaries normal. Suspension of uterus and appendectomy in addition to presacral sympathectomy. Pain entirely relieved.

CASE 5.—Patient aged twenty-two years, single, operation Oct. 30, 1934. Pelvic organs normal. Root of mesocolon displaced to right, making exposure of nerve difficult. Only slight relief of pain during the first two periods after operation. Since then pain has decreased so that now it is controlled by mild sedatives and patient is no longer incapacitated from work.

CASE 6.—Patient aged twenty years, married, nullipara, operation Nov. 14, 1934. Left salpingo-oophorectomy had been performed a year previously with no relief. The right adnexa and uterus were normal. She now has a "heavy feeling in the abdomen" and slight pain during the first day of the flow. Menstrual and intermenstrual backache persists.

CASE 7.—Patient aged twenty years, single, operation Nov. 27, 1934. Pelvic organs normal. Exposure of nerve complicated by displacement of mesocolon to the right.

Central, colicky dysmenorrhea has been entirely relieved by operation. During the four subsequent periods, she had bilateral pelvic pain of moderate severity, and the last two periods have been practically painless.

## CONCLUSIONS

1. This experience, combined with that of others reported in the literature, justifies the belief that presacral sympathectomy has a place in the treatment of properly selected cases of functional dysmenorrhea, but its adoption is warranted only when less radical measures have failed.

2. In organic dysmenorrhea, presacral sympathectomy may be used with advantage to supplement operations on the pelvic organs.

3. Ordinarily, the operation is not difficult, but conditions may be encountered rendering its performance not only tedious but also hazardous.

4. The operation relieves pain in the majority of cases and does not interfere with menstruation, spontaneous parturition, or motor control of the bladder and rectum.

## REFERENCES

*Adson, A. W., and Masson, J. C.:* J. A. M. A. **102:** 986, 1934. *Behney, C. A.:* Ann. Surg. **101:** 411, 1935. *Cotte, G., and Dechaume, M.:* J. de Chir. **25:** 653, 1925. *Cotte, G.:* Chirurgie du sympathique pelvien en gynecologie, Paris, Masson, 1932. *Cotte, G.:* Zentralbl. f. Gynäk. **57:** 1, 1933. *Counsellor, V. S., and Craig, W. McK.:* Am. J. Obst. & Gynec. **28:** 161, 1934. *Davis, A. A.:* Brit. M. J. **2:** 1, 1934. *DeCourcy, J. L.:* Am. J. Surg. **23:** 408, 1934. *Fontaine, R., and Hermann, L. G.:* Surg. Gynec. Obst. **54:** 133, 1932. *Gask, G. E., and Ross, J. P.:* Surgery of the Sympathetic Nervous System, Baltimore, 1934, William Wood and Company. *Greenhill, J. P., and Schmitz, H. E.:* J. A. M. A. **101:** 26, 1933. *Kuntz, A.:* The Autonomic Nervous System, Ed. 2, Philadelphia, 1934, Lea and Febiger. *Learmonth, J. R., and Braasch, W. F.:* Surg. Gynec. Obst. **51:** 494, 1930. *Learmonth, J. R.:* Brain **54:** 147, 1931. *Leriche, R., and Fontaine, R.:* Presse méd. **34:** 1121, 1926. *Rein, G.:* Soc. de Biol. 1882. *Wetherell, F. S.:* Am. J. Obst. & Gynec. **29:** 334, 1935.

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**Klaften, E.: Theory and Results of Vaginal Insulin Treatment of Cervical Erosions,** Med. Klin. **31:** 44, 1935.

During the last year Klaften has treated a large number of cervical erosions regardless of their etiology by means of intravaginal applications of insulin. This treatment has yielded excellent results. He observed that it delayed menstruation between two and nine days but he never noted any symptoms of hypoglycemia following the treatment. Even though there is some absorption of the insulin placed in the vagina, this form of therapy cannot be employed for diabetes. The good effects obtained in cases of cervical erosion are the result of local action and not of the absorbed insulin. Of course, one must be certain that the area to be treated is not a carcinoma.

Good results followed insulin application both in the form of a solution and as tablets. Both forms of therapy affected the ovaries as evidenced by the delays in menstruation. Hypodermic injections of insulin act in the same way on the ovaries but in a much more pronounced form.

J. P. Greenhill.

# THE PLACE OF COLPECTOMY IN THE TREATMENT OF UTERINE AND VAGINAL PROLAPSE

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THE term prolapse, when used in a general sense, denotes the descent of the uterus, bladder, urethra, rectum, and occasionally the culdesac of Douglas, through the vaginal introitus. When used in a limited sense, prolapse may refer to the extrusion of individual organs such as the

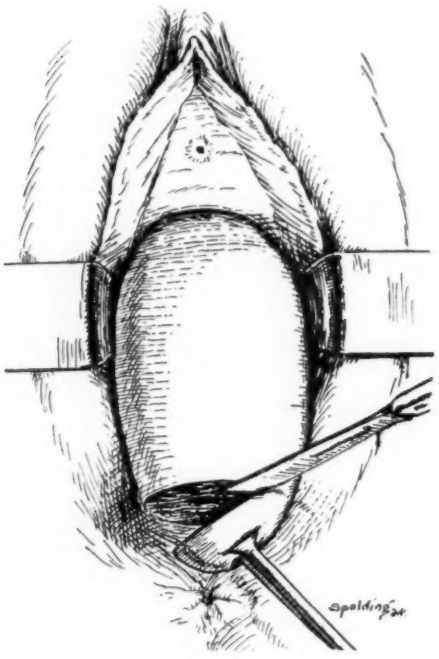

Fig. 1.

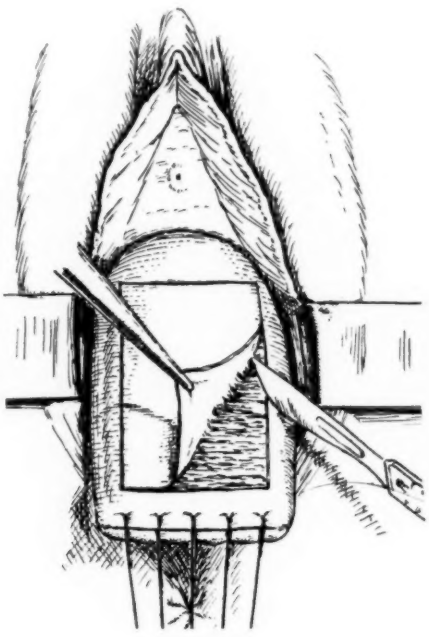

Fig. 2.

Fig. 1.—Subtotal Colpectomy. The cervix is dilated, the uterine cavity is curetted, the cervix, if eroded or lacerated, is amputated and reconstructed by means of chromic catgut sutures. When dealing with a prolapsed cervical stump, this is entirely removed and the edges of the vaginal wall are approximated with chromic catgut sutures. (LeFort)

Fig. 2.—Subtotal Colpectomy. The prolapsed cervical stump has been removed and the vaginal wall approximated by chromic catgut sutures. A rectangle of vaginal mucosa on the anterior vaginal wall has been outlined and is in process of being resected. (LeFort)

bladder or cystocele, the urethra or urethrocele, the rectum or rectocele, and the culdesac of Douglas or posterior vaginal enterocele. The term prolapse, in this paper, is used in its general sense.

While palliative measures such as pessaries and other mechanical measures may give relief in prolapse, surgery is the only curative method.

Surgical procedures are divided into two general classes: (1) the combined operation consisting of repair or amputation of the cervix, anterior and posterior colporrhaphy, and perineorrhaphy, followed by an abdominal operation as shortening of the uterosacral ligaments, uterine suspension or fixation, or supracervical hysterectomy with fixation of the stump, etc. (2) The vaginal operations, such as the interposition operation, vaginal hysterectomy with the interposition of the united broad ligaments (Mayo technic), and the high vaginal fixation of the uterus which Curtis[1] describes in his Textbook as the advancement operation, are three in common use although there are others. A proper repair of the pelvic

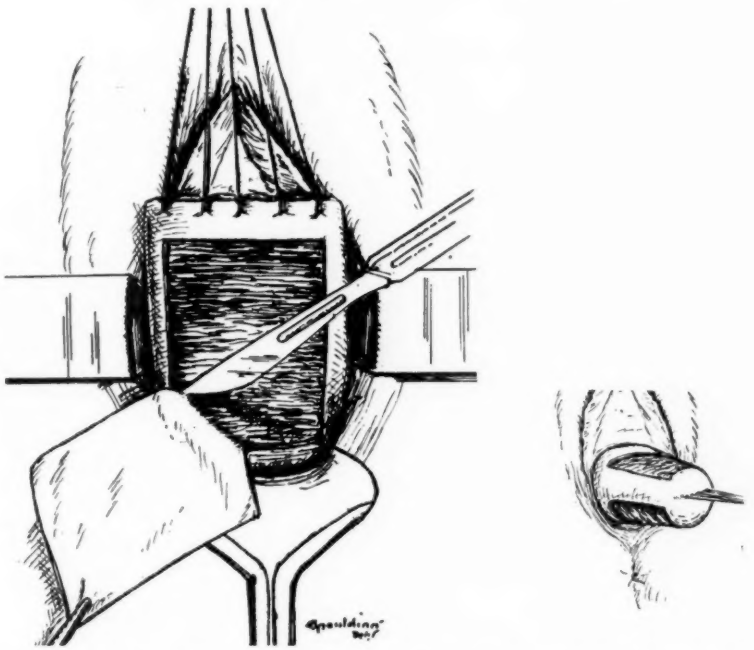

Fig. 3.—Subtotal Colpectomy. A rectangle of vaginal mucosa on the posterior vaginal wall has been outlined and is in process of being resected. The anterior and posterior rectangles should be of uniform dimensions. The insert shows the completed dissection. (LeFort)

floor is a complement to all the vaginal methods. George Gray Ward[2] has emphasized the fact that a hernia of the culdesac of Douglas should be attended to by resecting the culdesac and approximating the uterosacral ligaments while operating for a relaxed or lacerated perineum. The vaginal procedures which are relatively free from shock and which give excellent results are selected by the majority of pelvic surgeons, especially when operating on older women. They are also responsible for increasing the operability in this group of cases as they may be performed with safety when one would hesitate to do a laparotomy.

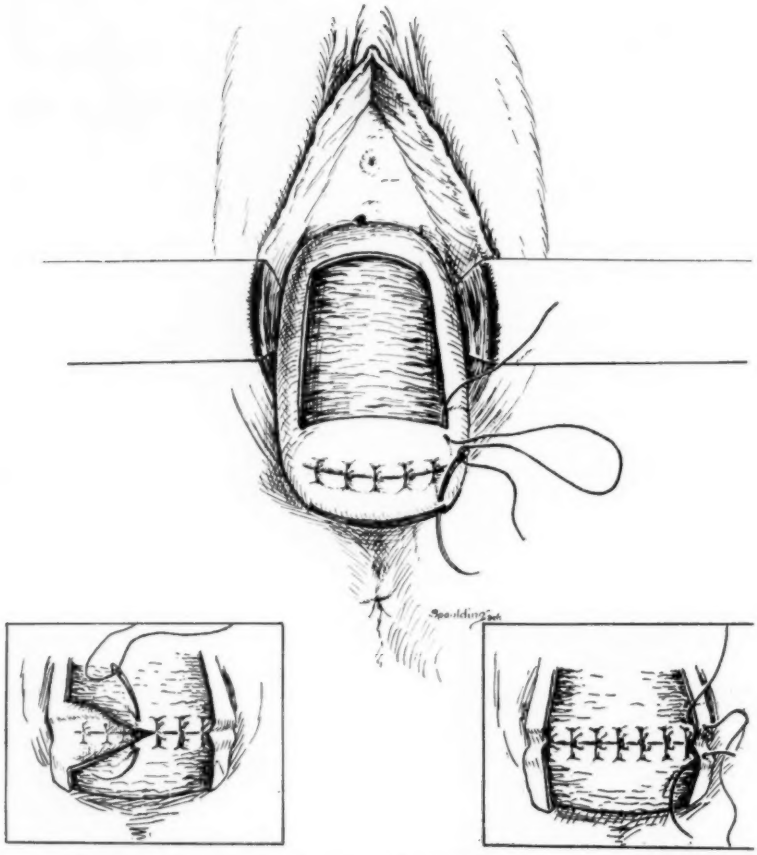

Fig. 4.—Subtotal Colpectomy. The inferior, then the lateral edges of the denuded areas are approximated by means of chromic catgut sutures. At the completion of this step of the operation, a superior and two lateral drainage canals, lined with vaginal mucosa, are formed. (LeFort)

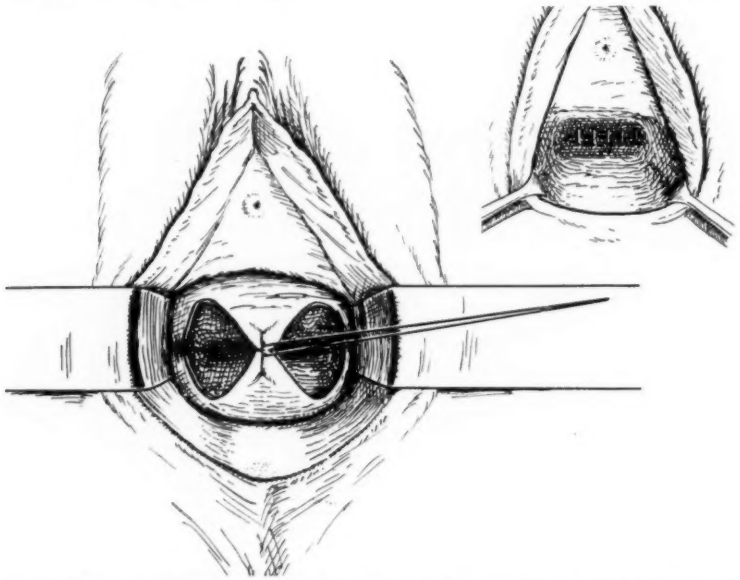

Fig. 5.—Subtotal Colpectomy. The superior edges of the denuded areas are now approximated with chromic catgut sutures. The prolapsed mass is now reduced. The insert shows this part of the operation completed. (LeFort)

While prolapse may be cured by the above mentioned methods, there is a group of women whose physical condition precludes the use of extended procedures and another group suffering from total inversion of

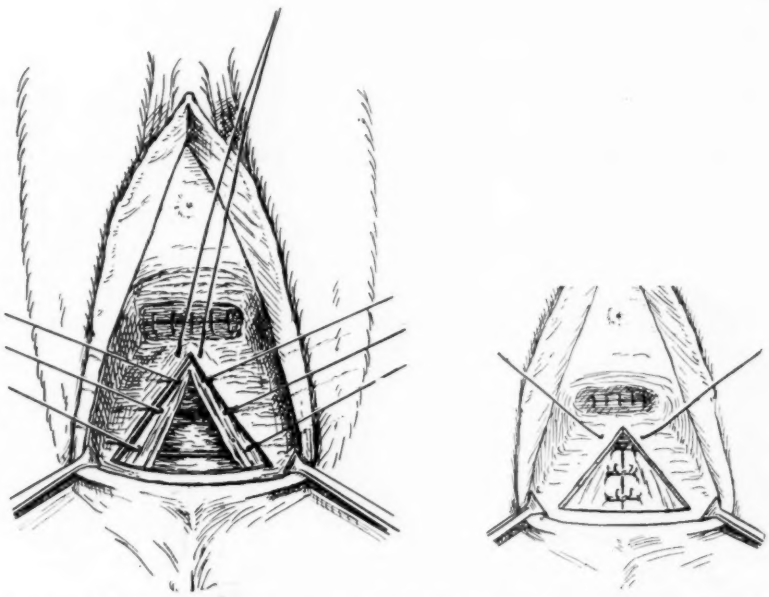

Fig. 6.—Subtotal Colpectomy. The perineum is denuded exposing the levator ani muscles and their covering fascia. The levators and their fascia are approximated by three chromic catgut sutures. The vaginal edges are next united by similar sutures. (LeFort)

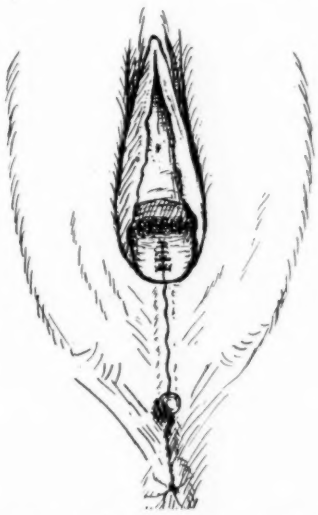

Fig. 7.—Subtotal Colpectomy. The external perineum is finished by a subcuticular stitch of fine chromic catgut, the end of which is held by a lead shot. The operation is completed. (LeFort)

the vagina following supracervical or total hysterectomy who are not easily cured by the ordinary methods. It is in this group of patients

that colpectomy, subtotal or total, plays its most important rôle. The operation is simple and may be performed with success even on poor surgical risks. Local infiltration anesthesia may be used to advantage if there is a contraindication to general or spinal anesthesia.

Léon LeFort[3] in 1877, described his operation, which is a subtotal colpectomy in which a rectangular area is denuded on the anterior and posterior walls of the prolapsed mass and the edges of these raw areas united by properly placed chromic catgut sutures. At the completion of the operation the cervix and corpus uteri are situated high above the newly constructed barrier. A superior canal below the cervix

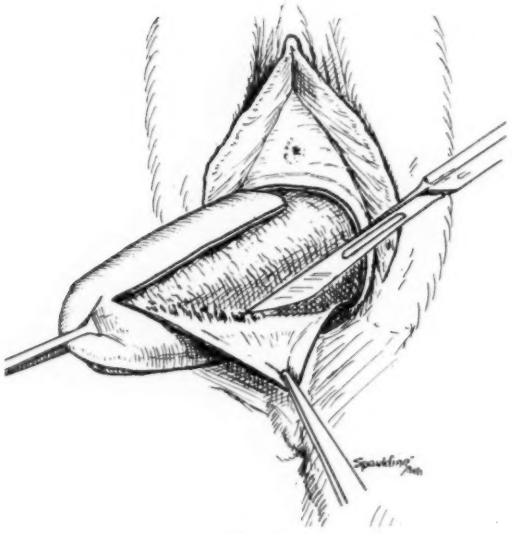

Fig. 8.

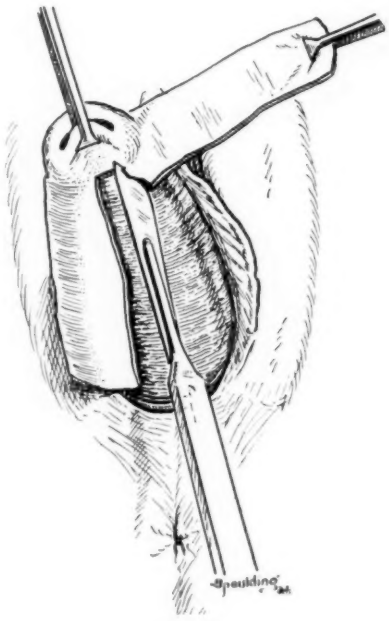

Fig. 9.

Fig. 8.—Total Colpectomy. Traction is made on the cervix and a circular incision is made in the vaginal wall about 2 cm. below the urinary meatus. An anterior and a posterior longitudinal incision is made in the median line, starting at the circular incision and ending a few centimeters from the cervix. The vaginal incisions must go through the entire thickness of the vaginal wall in order to find the line of cleavage between the bladder and the rectum and the vaginal wall. One side of the vagina is dissected free from its attachments. (Dujarier and Larget)

Fig. 9.—Total Colpectomy. One-half of the vagina has been dissected and is now resected from the cervix. The other half of the vagina is treated in a like manner. Care should be taken to excise small fragments of vaginal musosa which might remain adherent to the denuded surface. (Dujarier and Larget)

and two lateral canals are left for the purpose of drainage. This operation has been enlarged upon by making the anterior and posterior rectangles wider than called for in the original procedure, thus increasing the width of the supporting column but narrowing the lateral drainage canals. Amputation of the cervix, when it is the seat of laceration, irritation, or erosion, is a necessity, and repair of the perineum, by approximating the levator muscles and their investing fascia in the middle line, further adds to the support.

Total colpectomy was devised by Dujarier and Larget and well described by Hartmann.[4, 5] In this case a circular vaginal incision is made slightly below the level

of the urinary meatus and another above the level of the cervix, the vaginal wall is incised in the middle line, anteriorly and posteriorly, these incisions joining the lateral ones, the vaginal wall is then entirely removed in two halves, the cervix is amputated, and the cervical lips approximated by interrupted sutures of chromic catgut. Twelve strands of silkworm gut are tied in the central catgut stitch and form a drain from the uterine cavity when the operation is terminated. The bladder and rectum are united in superimposed layers by fine sutures of chromic catgut. Finally, the edges of the circular vaginal incision, below the urinary meatus, are united by interrupted sutures of No. 2 chromic catgut. The prolapsed mass is thus

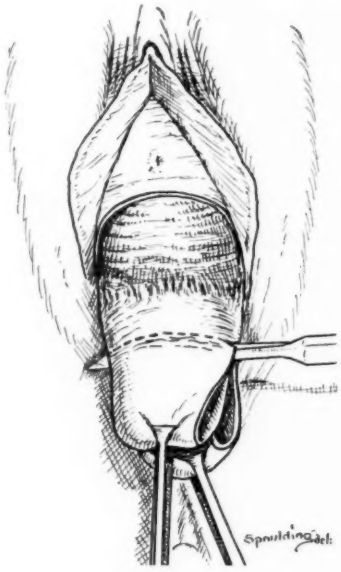

Fig. 10.

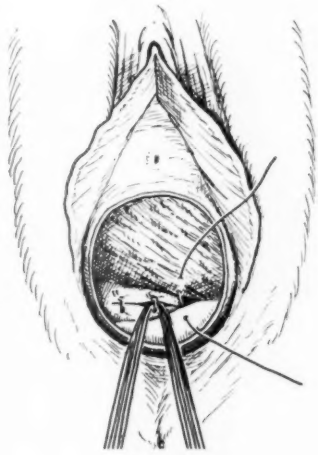

Fig. 11.

Fig. 10.—Total Colpectomy. The two halves of the vagina have been removed. The cylinder, making the prolapse, is entirely denuded up to the cervix. The uterovesical ligament is cut and the bladder is separated from the uterus. The cervix is next split with a knife and the anterior and posterior lips are amputated in the order mentioned. The cervical lips are united with three chromic catgut sutures. About twelve strands of silkworm gut are tied in the central stitch, over the cervical canal, and act as a drain. (Dujarier and Larget)

Fig. 11.—Total Colpectomy. The silkworm gut drain is shown. The bladder and rectum are united with sutures of fine chromic catgut, care being taken that the needle does not perforate these organs. Two or three planes of sutures are usually sufficient to reduce the prolapsed mass. (Dujarier and Larget)

reduced and the vagina completely closed around the silkworm-gut drain. The drain usually falls out on the tenth postoperative day. The perineum is repaired as after the subtotal colpectomy or LeFort operation. The majority of patients are treated by subtotal colpectomy while total colpectomy is reserved for extreme cases. In either instance, a diagnostic curettage should be performed to rule out endometrial carcinoma before resorting to the intervention.

Two objections to colpectomy have been expressed: (1) the inaccessibility of the uterus for treatment, should carcinoma develop at a later date; (2) the obliteration of the vaginal tube, precluding sexual relations. It is a recognized fact that carcinoma seldom develops in an

atrophied uterus and, since colpectomy is usually done on women whose uteri have undergone senile atrophy, the possibility of the development of carcinoma is very slight. The protection against carcinoma is increased by amputating the cervix, thus removing that part of the uterus on which malignant disease more frequently occurs. When this operation is performed on women who have had supracervical hysterectomies, removing the retained cervix as a preliminary step eliminates entirely the danger of carcinoma of the stump. The closure of the vagina in

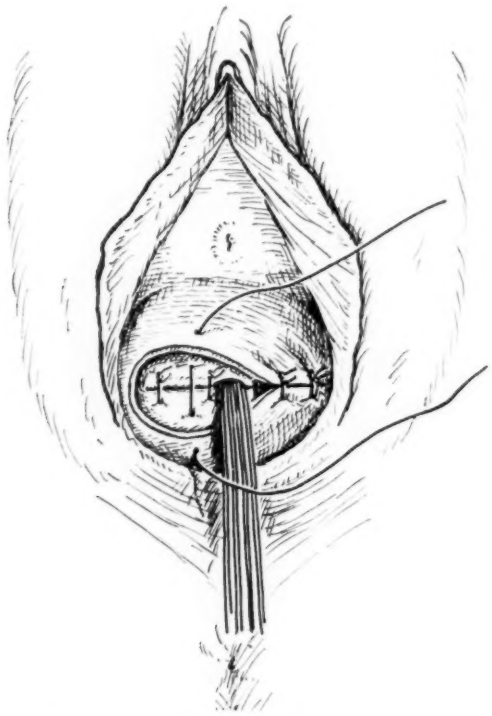

Fig. 12.—Total Colpectomy. The edges of the vaginal walls are approximated with sutures of chromic catgut. The silkworm gut drain allows the escape of blood and serum and also allows the persistence of a small drainage canal, permitting the escape of uterine secretions, should any form. (Dujarier and Larget)

Although the original operation does not call for it, a perineorrhaphy may be added with considerable advantage.

old patients suffering from total prolapse of the uterus offers no serious objection, since the sexual life of these women is of no great importance. Except under very rare exceptions, colpectomy should not be employed in the younger group of women still sexually active.

The technic of subtotal colpectomy and of total colpectomy, for the sake of clearness, is described by means of drawings and accompanying legends.

I desire to present herewith my results in a series of twenty-five personal cases.

STATISTICS

COLPECTOMY

| | |
|---|---|
| Subtotal colpectomy (LeFort). Enlarged | 20 |
| Total colpectomy (Dujarier and Larget) | 5 |
| Total | 25 |

SUBTOTAL COLPECTOMY

LeFort operation 20 cases

AGES

| | | |
|---|---|---|
| 45 to 49 years | 2 | |
| 50 to 54 years | 2 | |
| 55 to 59 years | 6 | |
| 60 to 64 years | 2 | |
| 65 to 69 years | 4 | |
| 70 to 74 years | 4 | 20 cases |

The youngest patient was 47 and the oldest 72 years of age.

INDICATIONS

| | | |
|---|---|---|
| Procidentia | 7 | |
| Recurrent procidentia | 3 | |
| Nulliparous procidentia | 2 | |
| Inversion of vagina following abdominal supracervical hysterectomy | 4 | |
| Inversion of vagina following abdominal panhysterectomy | 2 | |
| Inversion of vagina with atrophied uterus | 2 | |
| Total | 20 | cases |

ADDITIONAL DIAGNOSES

| | | |
|---|---|---|
| Posterior vaginal hernia (large) | 4 | |
| Calcified tumor of right ovary | 1 | |
| Ulceration of vagina | 1 | |
| Ulceration of cervix | 4 | |
| Ankylosis of both knees | 1 | |
| Total | 11 | cases |

OPERATION

| | |
|---|---|
| LeFort operation (enlarged) | 20 |
| Amputation of cervix | 5 |
| Perineorrhaphy | 19 |

In the case of one woman, sixty-six years of age, who had a nulliparous prolapse, the cervix was amputated, the LeFort operation was performed but the perineum was not repaired as it gave good support.

ANESTHESIA

| | | |
|---|---|---|
| Local anesthesia | | 5 |
| Spinal anesthesia | | 5 |
| General anesthesia (ether) | | 10 |
| | Total | 20 cases |

RESULTS

| | | |
|---|---|---|
| Mortality | | 0 |
| Recurrences | | 2 |
| Satisfactory results | | 18 |
| | Total | 20 cases |

RECURRENCES

2 recurrences in 20 cases, or 10 per cent.

CASE 8.—A woman, sixty-five years of age, who had an enormous procidentia, an atrophied uterus, a large cystocele, a large rectocele, and a large hernia of the culdesac of Douglas, was operated upon on December 7, 1927. As a result of the marked atrophy and poor blood supply of the vaginal walls, low grade sepsis set in and the union of the flaps was poor. The cervix appeared at the vulva, after healing by second intention had taken place. On March 9, 1928, a laparotomy was performed. A calcified tumor of the right ovary, 7.5 by 7.5 cm. approximately, was removed, together with the right tube, and the uterus was fixed to the anterior abdominal wall by three linen sutures. At the time of the last examination, the uterus was held against the anterior abdominal wall, there was no prolapse of the uterus, bladder, rectum, or culdesac of Douglas and the patient was getting along comfortably.

CASE 18.—A woman, sixty-one years of age, had a total inversion of the vagina following an abdominal panhysterectomy. She was operated upon on June 1, 1931, the LeFort operation and a perineorrhaphy being performed. On June 8, the vagina had to be packed because of secondary hemorrhage. On June 15, secondary hemorrhage recurred and the vagina was packed again. Healing took place by second intention but the result was only fair.

TOTAL COLPECTOMY

5 Cases

Ages—57, 59, 62, 64, and 64 years

INDICATIONS

1. Procidentia, small atrophied uterus, marked ulceration of cervix, enormous posterior vaginal hernia.
2. Inversion of vagina following abdominal supracervical hysterectomy, severe erosion of the cervix.
3. Inversion of vagina following abdominal supracervical hysterectomy, five previous operations for prolapse.
4. Procidentia, deep ulceration of the cervix.
5. Inversion of vagina, large posterior vaginal hernia.

OPERATION

| | |
|---|---|
| Total colpectomy | 5 |
| Amputation of cervix | 5 |
| Perineorrhaphy | 5 |

ANESTHESIA

| | |
|---|---|
| Local anesthesia | 1 |
| Spinal anesthesia | 2 |
| General anesthesia (ether) | 2 |

COMPLICATIONS

CASE 5.—A feeble woman, sixty-four years of age, had a recurrent procidentia following vaginal plastics and uterine suspension performed twenty-seven years previously; this was accompanied by total inversion of the vagina and a large posterior vaginal hernia. On March 17, 1930, a total colpectomy, amputation of the cervix and a perineorrhaphy were performed under spinal anesthesia. Healing took place satisfactorily and she was discharged with a good result. On Aug. 6, 1930, she had a purulent discharge escaping from the central drainage tract. Under spinal anesthesia a sound was introduced in the sinus and, at a depth of about 10 cm. an abscess was broken into with the escape of about 90 c.c. of thick green pus. The central canal was dilated and gently curetted; the material removed was examined histologically and reported as granulation tissue. The sinus was irrigated daily until clean, after which it readily healed. Examination several months after her discharge from the hospital showed a good result.

RESULTS

| | |
|---|---|
| Mortality | 0 |
| Recurrences | 0 |
| Satisfactory result | 5 |

CONCLUSIONS

1. Colpectomy as devised by Léon LeFort, in 1877, had been almost given up for years. More recently, the operation has been revived and somewhat modified in technic.

2. In old women colpectomy, subtotal (LeFort) or total (Dujarier and Larget), gives excellent results without subjecting the patient to undue operative risks.

3. Because of its benignancy and the simplicity of its performance, colpectomy permits increasing the operative incidence in these women.

4. Inversion of the vagina following supracervical or total hysterectomy may be easily cured by colpectomy.

5. Colpectomy may be performed under local infiltration or spinal anesthesia when general anesthesia is contraindicated.

6. A proper repair of the pelvic floor adds to the efficacy of the operation.

7. The end-results of twenty-five personal cases are reported.

REFERENCES

(1) *Curtis, A. H.:* A Textbook of Gynecology, Philadelphia, London, 1934, W. B. Saunders Co., pp. 239-252. (2) *Ward, G. G.:* J. A. M. A. **79:** 709, 1922. (3) *LeFort, Léon:* Bull. gén. de thérap. **92:** 337, 1877. (4) *Hartmann, Henri:* Gynéc. et Obstét. **11:** 452, 1925. (5) *Dujarier and Larget:* J. de chir. **25:** 283, 1925. (6) *Brocq, P., and Nora, G.:* Gynéc. et Obstét. **11:** 338, 1925. (7) *Crousse, R.:* Bruxelles-méd. **14:** 392, 1929. (8) *Bellas, J. E.:* Am. J. Surg. **25:** 258, 1934. (9) *Rubovits, W., and Litt, S.:* AM. J. OBST. & GYNEC. **29:** 222, 1935.

270 COMMONWEALTH AVENUE

# ANALYSIS OF END-RESULTS OF LABOR IN PRIMIPARAS AFTER SPONTANEOUS VERSUS PROPHYLACTIC METHODS OF DELIVERY

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EVALUATION of end-results of obstetric practice by the usual standards, maternal and fetal mortality, and the incidence of pelvic infections which have caused elevation of temperature, fails to take into account many serious accidents and complications of labor and delivery.

It is a well recognized fact that mortality statistics, although positive in themselves easily obtained, present a very incomplete picture of the handling of groups of obstetric patients. Furthermore, conditions such as the toxemias of pregnancy, hemorrhage, surgical shock, or severe birth injuries may leave a patient with less margin of safety, and more permanent discomfort and disability, than most pelvic infections which are justly regarded with so much concern.

It is self-evident that our aim should be to develop and apply methods which will not only reduce the incidence of mortality in mothers and babies, but will also prevent accidents, complications, and birth injuries which may either immediately be dangerous or productive of physical handicaps in after life.

The Obstetrical Department at the Woman's Hospital was opened in 1917. From the beginning, members of the staff have delivered an increasing percentage of patients by methods which have since come to be known as prophylactic. The impression has been that by these methods the incidence of birth injuries and complications to both mothers and babies has been reduced. In view of all the discussion for and against such obstetric procedures, the time seemed opportune to make a comparative study of end-results of labor and delivery, especially in cases delivered by spontaneous and prophylactic methods.

Cases used in the study were 2,800 primiparas, delivered on our ward service during the years 1920 to 1925, inclusive, and from 1930 to 1934, inclusive. Patients delivered in the earlier years were selected for comparison with patients delivered more recently, because in those years a large percentage was allowed to deliver spontaneously. In the later years, 1930 through 1934, a higher percentage of patients was delivered by prophylactic methods. Only primiparas were studied, for the obvious

reason that whatever permanent birth injuries were found, following delivery, could be directly attributed to the delivery. This gave an opportunity to make a more or less exact comparison of end-results after the various methods.

It is of interest that over 95 per cent of the patients in the series were delivered by hospital internes. The remaining 5 per cent were delivered by an attending surgeon, or an interne under supervision of an attending surgeon. In other words, the study is of the end-results of a system of obstetric practice in a hospital service equipped for gynecology and obstetrics. The actual work upon which the results are based has been almost entirely done by 88 hospital internes being trained in gynecology and obstetrics.

Table I shows age distribution, in percentages, of the cases studied.

TABLE I. AGE DISTRIBUTION OF 2,800 PRIMIPARAS

| AGE | PER CENT |
|---|---|
| Up to 20 | 10 |
| 20 to 25 | 42 |
| 25 to 30 | 31 |
| 30 to 35 | 12 |
| 35 to 40 | 4 |
| Over 40 | 1 |

As cases were studied, they divided themselves naturally into six distinct groups according to the methods of delivery employed:

1. Spontaneous
2. Spontaneous after perineal incision
3. Perineal incision and elective low forceps
4. Operative
5. Operative after perineal incision
6. Patients delivered by the abdominal route

Patients delivered by "elective low forceps" are those who would have delivered spontaneously if allowed to do so. All other forceps deliveries referred to later as "indicated forceps operations" were necessary for the protection of the mother, of the baby, or of both.

Midline perineal incision is now used almost routinely in the delivery of primiparas because: (1) It is easier to repair and is more likely to heal by primary union; (2) it avoids injury to the levator muscle.

The disadvantage of the midline incision is that if extension occurs, the anal sphincter and rectal mucosa may be injured. In this series, extension partially through the sphincter occurred in 4.4 per cent and completely through the sphincter in 3.2 per cent. No case in the series had fecal incontinence as a result of loss of sphincter control. One patient had a small rectovaginal fistula.

The technic used in the closure of perineal wounds has been exactly like that described by Goff for secondary repair of lacerations of the pelvic floor and posterior vaginal wall. It will be noted that the perineal body is repaired by catgut sutures, which are entirely subcutaneous. We believe that through and through nonabsorbable sutures, frequently used in the primary repair of perineal incisions or lacerations, predispose to infection and cause unnecessary discomfort.

It is self-evident that the benefits, to be derived from elective low forceps, may be lost and unnecessary or irreparable damage may be done, unless the procedure is used under satisfactory conditions, and by an operator with sufficient ability and training to: (1) Make an exact

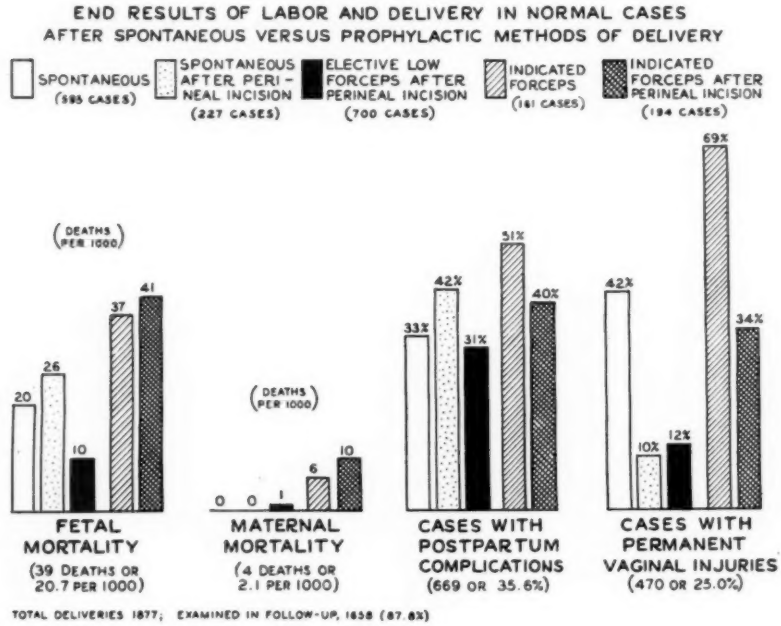


Chart 1.

diagnosis of the presentation, position and level of the presenting part. (2) Apply forceps correctly, and deliver the baby with a minimum of trauma.

We wish to emphasize the fact that elective forceps operations should not be done until, as Dr. Lee advises, "the head has come well down on to the pelvic floor, in complete anterior rotation, and has begun to part the levator ani pillars."

Physical findings noted in the follow-up were used as a basis for comparison of end-results in patients delivered by the various methods. Approximately 88 per cent of patients delivered were examined, at least once, six weeks after delivery by one or more attending surgeons who were specializing in gynecology as well as obstetrics.

All cases showing laceration or definite relaxation of the pelvic floor or vaginal walls were considered abnormal.

A summary of the end-results of labor and delivery in 1,877 normal cases is shown in Chart 1. This group included only women with normal pelves who went into labor spontaneously at term, with a vertex presentation, an anterior position, or a posterior position with spontaneous rotation.

We note that:

1. The incidence of fetal mortality and postpartum complications, in patients delivered by elective low forceps after perineal incision, was lower than in spontaneous deliveries.

2. Perineal incision, whenever used, strikingly reduced the incidence of cases, with permanent birth injuries.

3. There was no maternal death in patients delivered spontaneously. One maternal death after elective low forceps was the result of sepsis caused by retained placental tissue.

The relatively high incidence of fetal and maternal deaths, postpartum complications, and patients with birth injuries which occurred in the 194 patients delivered by indicated forceps after perineal incision as compared with the 161 patients delivered by forceps alone, can be explained by two facts as follows: (1) In the group delivered by forceps alone, 65 per cent had prolonged labors as compared with 87 per cent in the other group. (2) End-results were undoubtedly influenced by the type of forceps operation required to complete the delivery as noted in Table II. From this table it will be noted that nearly twice as many patients were delivered by midforceps after perineal incision as in the group delivered by forceps alone.

TABLE II. NORMAL CASES. SUMMARY, IN PERCENTAGE, OF THE VARIOUS TYPES OF OPERATION REQUIRED IN PATIENTS DELIVERED BY INDICATED FORCEPS

| TYPE OF FORCEPS OPERATION | METHOD OF DELIVERY | |
|---|---|---|
| | FORCEPS NO. OF PATIENTS 161 | FORCEPS AFTER PERINEAL INCISION NO. OF PATIENTS 194 |
| Low | 77 | 60 |
| Mid | 22 | 39 |
| High | 1 | 1 |

The relatively low incidence of fetal mortality, associated with delivery by prophylactic low forceps, is significant. It is fair to assume that any method of delivery which is attended by a low incidence of fetal mortality, is also attended by a correspondingly low incidence of babies with birth injuries which are not fatal. Unfortunately, the babies delivered in this series could not be followed for a sufficient period of time to confirm this assumption.

In Chart 2 is demonstrated to what extent and how consistently perineal incision is a prophylactic measure in preventing permanent vaginal birth injuries in various types of cases.

Normal cases, with prolonged labor, were selected by the same standards as those in Chart 1, but were studied separately to determine the effect of prolonged labor in the causation of vaginal injuries.

In the prolonged group were included all normal cases in which labor had not terminated within twenty-four hours, or in which the second stage had exceeded two hours in duration. From this it is evident that the pressure of prolonged labor may in itself be an important factor in the causation of permanent vaginal birth injuries.

It also shows the end-results following delivery at term of 227 women with contracted pelves causing excessive pressure during labor and a

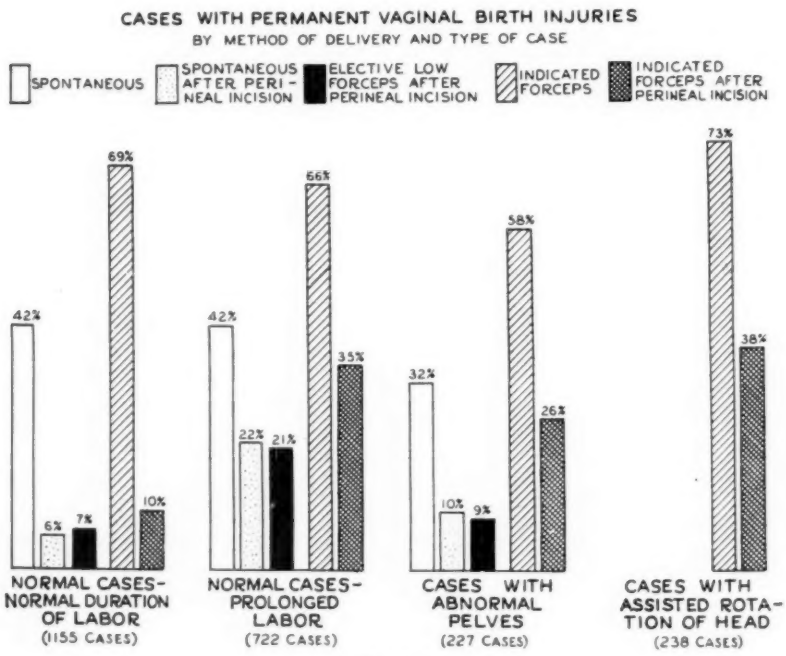


Chart 2.

definite increase in vaginal injuries as compared to end-results in cases with normal pelves.

Although statistics are not recorded on this chart, the relationship of the size of the baby to the incidence of birth injuries was studied and showed convincing evidence that excessive pressure from large babies was another definite factor in the causation of vaginal birth injuries.

The incidence of cervical lacerations varied from 34 to 46 per cent in the various types of cases and the uterus was found to be retroverted in from 16 to 25 per cent of the cases in the various groups studied.

Of the 238 patients with persistent occiput posterior position, 6 were delivered as occiput posterior, and in the remaining 232 patients, rotation was accomplished as follows: manual 55, Scanzoni 155, and Kielland 22. Following rotation 5 babies were delivered spontaneously. Of

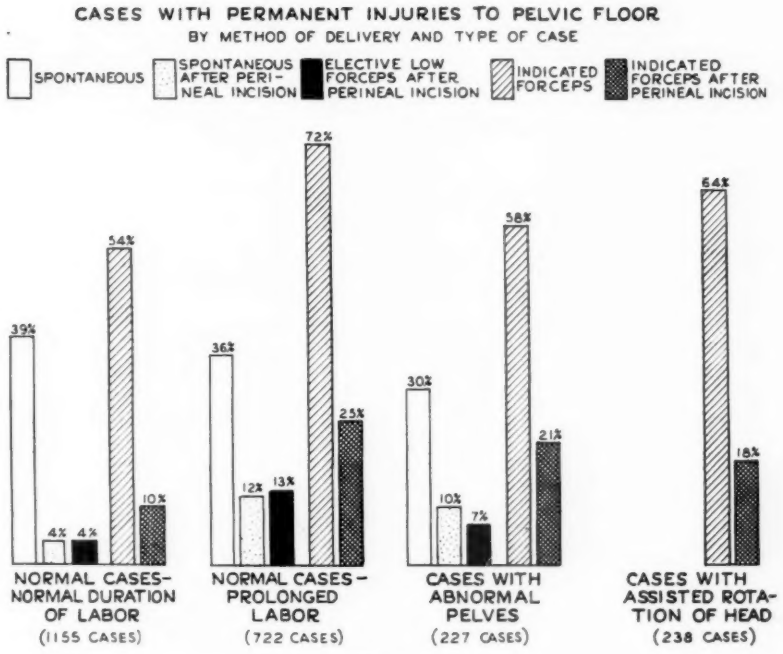


Chart 3.

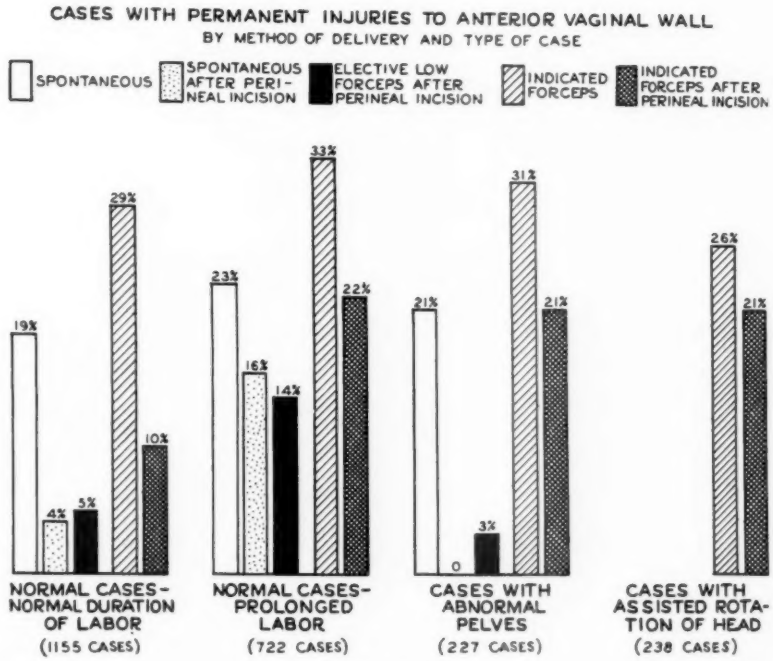


Chart 4.

the 233 delivered by forceps, operations were classed as follows: low 60, mid 157, and high 16. The number of patients delivered as occiput posterior was too small to be recorded.

The graphs shown in Chart 3 demonstrate in a rather striking way to what extent prophylactic methods of delivery prevent permanent injuries to the pelvic floor in various types of cases.

From Charts 4 and 5 it is evident that perineal incision greatly reduces the incidence of permanent injuries to the anterior and posterior vaginal walls. These graphs indicate that the procedure is as effective in preventing injuries to the anterior wall as it is to the posterior wall. A comparison of the two indicates that in prolonged labor the percentage

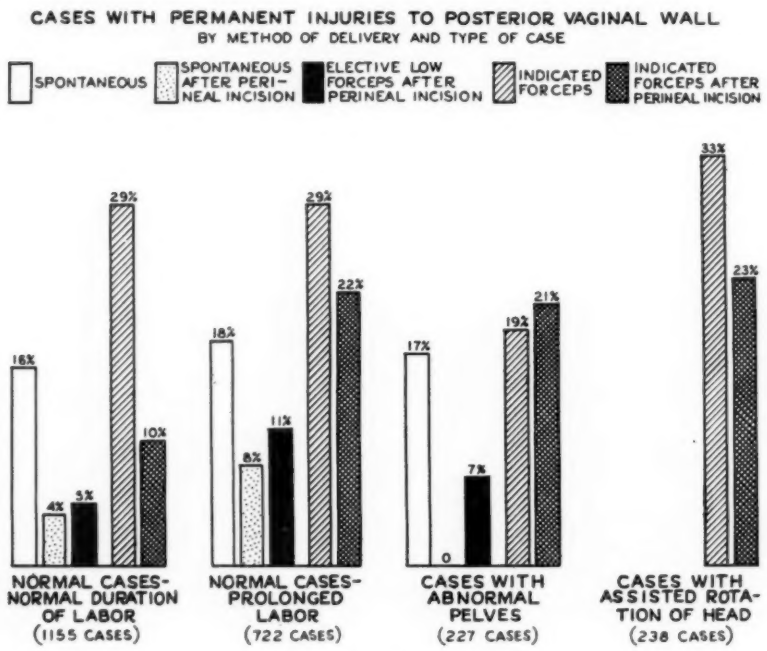


Chart 5.

of patients with injuries to the anterior wall increases more than does that of injuries to the posterior wall.

The incidence of vaginal injuries in breech deliveries is shown in Chart 6 and indicates that perineal incision is a prophylactic measure in every type of delivery.

In this group are included 94 patients who presented as breech and 28 patients who were delivered by version and extraction.

A comparison of physical findings, during the early days when a high percentage of patients was allowed to deliver spontaneously, with those of later days when a high percentage was delivered by prophylactic methods, is not an entirely fair or accurate one, for in the early days certain injuries to the cervix and pelvic floor and permanent relaxations of the

vaginal walls were considered inevitable and therefore within normal limits. We now consider injuries to the pelvic floor and vaginal walls to be preventable in such a high percentage of cases, that they are recorded as definite birth injuries, rather than physiologic changes incidental to delivery.

It is now our custom to discharge from our follow-up six weeks after delivery, patients free from birth injuries. Large numbers of patients kept under observation for long periods of time have convinced us that the result at six weeks so rarely changes, that it can be considered a final one.


Chart 6.

Patients with postpartum cervical injuries and erosions are treated with electrocoagulation, and such patients are kept under observation until healing is complete. Retroversion is treated with posture and in some patients with pessaries. We find that if the vaginal walls are not abnormally relaxed by delivery, pessaries large enough to give proper support are difficult to insert. Consequently, we have used fewer pessaries since more patients have been delivered by elective methods.

Table III is a summary of cases delivered by the abdominal route and results obtained.

Of the 2,800 primiparas selected for this study, 82 or 2.9 per cent were delivered by the abdominal route. In the past few years, since the advantages and relative safety of low flap and extraperitoneal (Latzko) cesarean section have been established, the classical operation is rarely

done, and the incidence of delivery by the abdominal route has increased to a point considerably higher than that shown in this series.

In the interest of both mothers and babies, we now consider cesarean section the method of choice for the delivery of women with obstructed labor from contracted pelvis, or cervical dystocia, and for those women in whom delivery is complicated by placenta previa. It is also used in selected cases for the delivery of women who are the victims of arrested tuberculosis, cardiac disease, or toxemia of pregnancy.

TABLE III. DELIVERIES BY THE ABDOMINAL ROUTE

| INDICATION | NUMBER OF CASES | TYPE OF CESAREAN | | | FETAL MORTALITY |
|---|---|---|---|---|---|
| | | CLASSICAL | LOW FLAP | LATZKO | |
| Contracted pelvis | 26 | 14 | 11 | 1 | – |
| Toxemia of pregnancy | 15 | 2 | 13 | – | – |
| Cervical dystocia | 15 | – | 11 | 4 | – |
| Obstructed labor | 5 | 1 | 4 | – | – |
| Disproportion | 5 | – | 4 | 1 | – |
| Tuberculosis | 5 | 1 | 4 | – | – |
| Placenta previa | 4 | 1 | 3 | – | 1* |
| Premature separation of placenta | 3 | – | 3 | – | 1† |
| Elderly primiparas | 2 | 1 | 1 | – | – |
| Cardiac disease | 1 | – | 1 | – | – |
| Full-term abdominal pregnancy (hysterectomy) | 1 | – | – | – | – |
| Total | 82 | 20 | 55 | 6 | 2 |

*Baby dead at term before operation.

†Baby macerated at twenty-eight weeks' gestation. No maternal mortality. Operations: Elective, 28; after trial labor, 54.

Intelligent use of cesarean section demands careful study of patients in the antepartum period and expert handling and observation in the early hours of labor. With a proper understanding of acceptable indications and a careful study of individual patients, we feel that of all sections done, the incidence of elective operations could be increased and that on the whole, the decision to deliver a patient by the abdominal route, after trial labor, might frequently and advantageously be made somewhat earlier.

Furthermore, we are now convinced that in the hands of men well trained in gynecology and obstetrics, cesarean section may be used as a method of delivery, in certain borderline cases, with sufficient safety to allow the welfare of the child to be considered.

Table IV presents a summary of all postpartum complications. The incidence of sapremia is high owing to the fact that the diagnosis was not based entirely on an arbitrary level of temperature. We believe that a slight but continued rise of temperature above normal is often more significant than fever to a level sufficient to be classed as "infectious morbidity" by most prevailing standards.

We believe that postpartum morbidity should mean more than postpartum infection.

A recently published study of postpartum complications at the Woman's Hospital showed that patients may have significant complications without any elevation of temperature. Again, we wish to emphasize the need for a logical uniform standard for the determination of puerperal morbidity. Such a standard should be based on a consideration of all symptoms and physical findings rather than on a single symptom, such as fever.

TABLE IV. SUMMARY OF POSTPARTUM COMPLICATIONS FOLLOWING VAGINAL DELIVERIES

| TYPE OF COMPLICATION | NUMBER OF CASES |
|---|---|
| Sapremia | 565 |
| Faulty wound union, pelvic floor | 210 |
| Mastitis, nonsuppurative | 110 |
| Urinary tract infections | 54 |
| Upper respiratory infections | 48 |
| Hemorrhage, 1° | 41 |
| Shock | 33 |
| Mastitis, suppurative | 18 |
| Hemorrhage, 2° | 16 |
| Fever, cause undetermined | 12 |
| Bronchitis | 11 |
| Pelvic infection | 10 |
| Thrombophlebitis | 6 |
| Pneumonia | 3 |
| Hemorrhage, 3° | 3 |
| Miscellaneous | 27 |

Table V shows the incidence of fetal mortality and causes of death in premature and mature babies. There was a total of 2,824 (mature 2,617, premature 207) babies born. Of these babies, 150 (mature 94, premature 56) were stillborn or died within the first two weeks of life. In estimating fetal mortality, Stander has recommended that all babies weighing less than 1,500 gm. and that are less than 35 cm. in length be excluded. By this standard the total number of babies born would be 2,796 and the total number of fetal deaths would be 122, making the rate for fetal mortality 4.3 per cent or 43 deaths per 1,000.

TABLE V. FETAL MORTALITY

| CAUSE OF DEATH | NO. OF DEATHS |
|---|---|
| Birth trauma | 54 |
| Cord pressure | 14 |
| Toxemia of pregnancy | 11 |
| Malformation | 7 |
| Premature separation of placenta | 6 |
| Infections | 6 |
| Atelectasis | 5 |
| Syphilis | 2 |
| Prematurity | 1 |
| Cause undetermined | 16 |
| Total | 122 |
| Total number of infants | 2,796 |
| Total number of fetal deaths | 122 |
| Percentage of fetal deaths | 4.3 |

Table VI is a summary of all maternal deaths in the series.

Two deaths occurred in patients who became septic following delivery. The first was in a woman who had had a severe hemorrhage from placenta previa before admission. Following vaginal delivery of a baby presenting as a breech she became septic and died suddenly of what was thought to be a pulmonary embolism on the twenty-fourth postpartum day. The other septic death occurred in a woman in whom, at time of delivery, a succenturiate placental lobe was accidentally left in the uterus. This was removed on the thirteenth postpartum day on account of hemorrhage. The patient developed a nonhemolytic streptococcic bacteremia and died on the thirty-sixth postpartum day.

Failure in recent years to reduce the incidence of maternal mortality continues to be a matter of great concern to obstetricians. In an accounting of the end-results of obstetric practice, perhaps attention has been too often focused on maternal and fetal mortality. Prevention of the serious complications, accidents, and birth injuries during labor and delivery, seems the logical means for reducing mortality. Again we are faced with the importance of antepartum care and the necessity for as careful preparation of the patient for delivery as would be demanded for any major surgical operation. The delivery should then be conducted in accordance with established surgical principles for the prevention of trauma, hemorrhage, surgical shock, and infection.

TABLE VI. MATERNAL DEATHS IN PRIMIPARAS

| AGE | ANTEPARTUM OBSERVATION | COMPLICATION OF PREGNANCY | GESTATION (WEEKS) | CAUSE OF DEATH | POSTPARTUM COMPLICATION |
|---|---|---|---|---|---|
| 33 | None | Placenta previa | 37 | Pulmonary embolism* | Secondary anemia |
| 38 | None | None | 40 | Pulmonary embolism | None, afebrile |
| 31 | Satisfactory | None | 40 | Pulmonary embolism | Furunculosis |
| 31 | Satisfactory | Cardiac disease | 40 | Lobar pneumonia | Lobar pneumonia |
| 29 | Satisfactory | Toxemia | 40 | Bacteremia* | Retained placental tissue (removed 13th p.p. day) |
| 37 | None | Chronic nephritis | 28 | Uremia | Uremia |
| 37 | None | Chronic nephritis | 24 | Uremia (died undelivered) | — |

Total number of deliveries—vaginal 2,718; abdominal 82; total 2,800.
Total number of deaths—7 (0.25 per cent) or 2.5 deaths per 1,000 births.
*Deaths from sepsis—2 (0.071 per cent) or 0.71 deaths per 1,000 births.

## CONCLUSIONS

1. The incidence of birth injuries to mothers and babies, and postpartum complications, were in direct proportion to the incidence of factors, such as prolonged labor, abnormal pelves, faulty presentation, and large babies, which resulted in the application of increased pressure to the maternal soft parts and to the fetus during labor and delivery.

2. Elective low forceps after perineal incision can justly be regarded as a prophylactic procedure in patients who would deliver spontaneously if allowed to do so.

3. Perineal incision when used in conjunction with any type of vaginal operative delivery consistently reduced the incidence of birth injuries and postpartum complications.

4. Prophylactic methods of delivery should be used by men trained both in obstetrics and gynecology in hospitals properly equipped to give obstetric care.

5. Ideally, all women should have the protection of delivery in hospitals under supervision of men trained in gynecology and obstetrics.

REFERENCES

*Ward, Goff, and Aldridge:* Bull. Am. Coll. Surg. **19**: 9, 1935. *Goff:* Surg. Gynec. Obst. **46**: 855, 1928.

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## CLINICAL AND BACTERIOLOGIC OBSERVATIONS IN TRICHOMONAS VAGINITIS

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DEFINITE proof is lacking as to which one of the many organisms found in the vaginal secretions of Trichomonas vaginitis is responsible for this condition.[1-5] The mode of primary infection is also still in need of explanation. The numerous and varied treatments which have been advised from time to time suggest that none of them is specific.[6-10] We have attempted in this study to correlate some of our clinical observations with bacteriologic data which we hope will be of interest in these problems.

*Symptoms.*—It has been shown repeatedly that trichomonas may be present in the vaginal secretion for long periods of time without producing symptoms. It would seem, therefore, that such individuals must have either developed an immunity to the infection or that there is lacking in these patients some additional element which would cause symptoms if present. It has been suggested by various investigators that this additional factor is most probably a streptococcus.[2, 3] Considerable evidence has already been produced which indicates that symbiotic union of a streptococcus and Trichomonas vaginalis is necessary for the production of symptoms.

When symptoms do occur they are usually characterized by an acute onset, often following conditions which result in lowered resistance. These low points in resistance may coincide with the menstrual period, respiratory infections, extreme fatigue, pregnancy, disturbances of the gastrointestinal tract, or sexual intercourse.

It has not been our experience that patients afflicted with Trichomonas vaginitis always present the clinical picture as it is usually described. The usual symptoms of vulvar itching and burning caused by the irritating vaginal discharge are frequently less severe than the urinary disturbances. Frequency of urination, dysuria, nocturia, and even incontinence are often so pronounced that the vaginal source of the disease may readily be overlooked. Our mistakes of diagnosis in this regard have been most frequent when the vaginal discharge was not profuse or when it retained its thick, mucoid or normal cheesy character. Several of our patients had been or were subjected to cystoscopy and pyelography before Trichomonas vaginitis was suspected.

During the course of the disease about one-fourth of our patients developed increased bleeding. This menorrhagia was often transitory and occasionally was associated with metrorrhagia. We do not believe that this increased blood loss can be ascribed alone to the unusual congestion in the pelvis. We are inclined to think that pelvic cellulitis secondary to Trichomonas vaginitis is a more common occurrence than is generally supposed. It is not unreasonable to suggest that these associated virulent streptococci may ascend the genital tract of women almost as readily as the gonococcus. Five of our patients had been examined vaginally before the onset of the menorrhagia and their pelves found to be normal. Following the appearance of increased blood loss, examination revealed palpable tender adnexal swellings. This inflammatory reaction was severe enough to cause an elevation of temperature, and in three of these patients a leucocytosis of 12,400, 17,600 and 20,200 developed. Repeated examinations failed to reveal the gonococcus. Further confirmatory evidence of the invasive tendencies of these streptococci was obtained by culturing material taken from two bartholinian abscesses. In both instances we were able to recover the same type of streptococcus as was found in cultures of the vaginal secretion. In an additional instance of acute bartholinitis, however, associated with Trichomonas vaginitis, we were unable to obtain any growth of bacteria.[8]

The clinical picture of one of these patients was to us particularly interesting. For a period of about three years there had been present an increased discharge from the vagina. On several occasions during this time, usually following the menstrual period, an acute exacerbation of the vaginitis had occurred. In the course of the last acute attack the right Bartholin gland had become tender and swollen to the size of a large English walnut. At the same time a

monarticular arthritis, involving the left wrist, developed. The complement fixation test was negative and repeated slide examinations of the vaginal secretions revealed *Trichomonas vaginalis* but no gonococci. Drainage of the bartholinian swelling followed by treatment of the vaginitis led to a slow but constant improvement in the pain and swelling of the wrist joint. Cataphoretic studies of the streptococci obtained from the Bartholin gland indicated that they were of the arthrotropic variety.

A rather large percentage of these women have exhibited arthritic and neuritic symptoms in other regions of the body. We shall attempt to indicate later in the discussion of the bacteriology that these focal infection syndromes may be due to associated bacteria of the streptococcus group. This evidence is further supported by the fact that some of these patients have been relieved of the joint and muscular symptoms by appropriate local or general treatment of the vaginitis.

We have tried most of the accepted methods of treatment with about the same average degree of success. Roughly, about 80 per cent of all of our patients have responded favorably and permanently to these various therapeutic measures. The remaining 20 per cent have had variable recurrent periods of infestation, some of them extending over a period of years. It is with this latter group that we have been particularly concerned and studies have been made along the following lines.

Bacteriologic studies have been made of the streptococci found in the vagina of patients suffering with Trichomonas vaginitis. At the same time similar cultures were taken from the nasopharynx. These cultures have been compared with cultures taken in the same manner from the vagina and nasopharynx of normal women.

We have compared the cultures obtained from patients responding readily to treatment with those in whom recurrences had occurred. Whenever possible we have searched for trichomonas in the prostatic secretion of the husbands of these women. In each case the culture of streptococcus obtained from the prostatic secretion has been compared with that isolated from the vaginal secretion of the wife. Attempts are being made to alleviate the condition by increasing the local and general resistance of these individuals.

All of these cultures were grown in tall columns of dextrose brain broth and on blood agar plates. The cultures were incubated for eighteen hours at 37° C. When colonies had been identified they were prepared for study in the cataphoretic cell. The apparatus used was a modified Northrop-Kunitz-Mudd assembly.

Many investigators[11-13] have demonstrated that bacteria carry electrical surface charges. When these bacteria are suspended in distilled water and an electrical current is passed through the cataphoretic cell, the organisms move toward the anode. On reversal of the current, move-

ment occurs toward the changed position of the anode. The velocity of this migration seems to indicate specificity and, therefore, helps to identify the organism.

Graphs have been prepared to represent the curves of the electrical potential. These graphs indicate that the streptococci isolated from the vagina of all patients afflicted with Trichomonas vaginitis fall in the same general area of electrical charge. By this method no difference in the electrical potential of the bacteria isolated from those patients responding readily to treatment and those exhibiting the recurrent and resistant infections could be determined. To us this fact seems to indicate that the difference between the transitory and resistant infection is more probably one of lowered resistance or reinfection of the host. These strains of streptococci were of the green-producing type. Especially in those patients complaining of joint and muscular symptoms cataphoretic examination of the cultures identified them as belonging to the group of arthrotropic or neurotropic streptococci.[11]

Streptococci cultured from a few normal vaginal secretions did not have the same electrical potential grouping as those from the vagina of affected cases. The cultures obtained from the nasopharynx of all patients have a distinctly different electrical potential grouping than those grown from normal or infected vaginal secretions. However, in one patient a strain was recovered from the substance of a tonsil after its removal which corresponded potentially with the strain isolated from the discharge caused by her Trichomonas vaginitis. Similar results were obtained in another patient where the material was secured from an infected tooth and compared with the bacteria from the infected vaginal secretion.[14]

The bacteria grown from the tooth and tonsillar tissue were injected into the blood stream of a rabbit. A suggestive localization in the cervix was noted. We have not been able, however, to infect the vagina of the rabbit with trichomonas either in its normal state or following intravenous inoculation with the specific strain of streptococci obtained from the infected human vagina.[15-19] We hope to investigate this possibility more thoroughly.

The most evident and logical source of reinfection should, of course, be sexual intercourse. Recently Dr. Norris J. Heckel has been cooperating with us in the prostatic examination of the husbands of patients having Trichomonas vaginitis. We have recovered trichomonas from the prostatic secretion in six of the husbands and in seven others have found evidence of a chronic prostatitis. The prostatic fluid has been cultured at the same time cultures were taken from the vagina of the wife. Streptococci of the same electrical potential have been ob-

tained in the nonspecific prostatitis without the trichomonas as in the secretion containing the flagellates. The graphs of the electrical potentials of the organisms from the prostatic secretions reveal that they are organisms similar to those found in the vagina. This finding has occurred with such regularity and under such suggestive conditions that we feel that both Trichomonas prostatitis and Trichomonas vaginitis may well be added to the list of venereal diseases.[20-23] Only three husbands in whom we were able to culture the prostatic secretion failed to reveal either the trichomonas or streptococci. The trichomonas disappear rapidly from the prostate with massage or by the application of heat. The streptococcal residue, however, is more resistant to treatment. Dr. Heckel has recently reported[24] some very encouraging results in the treatment of the more acute forms of streptococcal prostatitis, and he expects to extend his work to include these chronic forms. Constant transfer of these streptococci from host to host may very well increase the virulence of the organism. Constant transfer of these virulent organisms may institute the initial vaginitis and the trichomonas may well be the secondary invaders.

An instructive case history may best illustrate the points under discussion. This patient had been treated for a period of several months during which time there were three recurrences. Following one of these periods of treatment the patient left for a six months' vacation. During her absence she was entirely free from symptoms. Seven days after her return she came to the office complaining of an acute return of the typical symptoms. Five days later the husband appeared complaining of dysuria and a slight urethral discharge. The prostatic and vaginal fluids contained swarms of trichomonas and on culture many streptococci of the same electrical potential were found.

Resistance of the host is always the most important factor in combating infection. The relatively good results of so many types of different treatments which have been suggested for Trichomonas vaginitis leave one with the impression that their general efficacy depends upon raising the local resistance of the vagina rather than the bactericidal properties of therapeutic agents employed.

We have attempted to raise the general as well as local resistance. Rest, both physical and sexual, has been suggested. Adequate vitamin intake has been maintained. Prompt treatment of respiratory and gastrointestinal difficulties has been instituted.

Following the suggestive results reported in arthritis, neuritis, and gonorrhea by the use of vaccines and filtrates,[24-27] we have begun to inject intracutaneously into these patients preparations obtained from their individual growths of bacteria. As yet only suggestive results have been obtained. We expect to report them more fully at a later date.

REFERENCES

(1) *Davis, C. H., and Colwell, C.:* J. A. M. A. **92:** 306, 1929. (2) *Hesseltine, H. C.:* Am. J. Obst. & Gynec. **26:** 46, 1933. (3) *Hibbert, J. F.:* Am. J. Obst. & Gynec. **25:** 465, 1933. (4) *Curtis, A. H.:* Surg. Gynec. & Obst. **18:** 299, 1914. (5) *Kleegman, S. J.:* Surg. Gynec. & Obst. **51:** 552, 1930. (6) Davis, C. H.: Am. J. Obst. & Gynec. **19:** 575, 1929. (7) *DeLee, J. B.:* Illinois M. J. **37:** 186, 1920. (7 A) *Stein, I. F., and Cope, E. J.:* Am. J. Obst. & Gynec. **24:** 348, 1932. (8) *Greenhill, J. P.:* Am. J. Obst. & Gynec. **16:** 870, 1928. (9) *Goodall, J. R.:* J. Canad. M. A. **25:** 292, 1931. (10) *Gellhorn, George:* J. A. M. A. **100:** 1765, 1933. (11) *Wood, W. L., Jensen, L. B., and Post, Wilber E.:* Ann. Int. Med. **8:** 734, 1923. (12) *Jensen, L. B.:* J. Infect. Dis. **37:** 481, 1926. (13) *Rosenow, E. C.:* J. Immunol. **26:** 401, 1934. (14) *Bumpus, H. C., and Meisser, J. G.:* J. Urology **5:** 249, 1921; also with *Meisser, J. G.:* Arch. Int. Med. **27:** 326, 1921. (15) *Bland, P. Brooke, Goldstein, L., Wenrich, D. H., and Weiner, Eleanor:* Am. J. Hyg. **16:** 492, 1932. (16) *Rakoff, A. E.:* Am. J. Hyg. **19:** 502, 1934. (17) *Rosenow, E. C.: Jordan and Falk's:* The Newer Knowledge of Bacteriology and Immunology, Chicago, 1928, University of Chicago Press, p. 576. (18) *Hegner, R.:* J. Parasitol. **14:** 261, 1928. (19) *Hegner, Robert: Jordan and Falk's:* The Newer Knowledge of Bacteriology and Immunology, Chicago, 1928, University of Chicago Press. (20) *Smith, J. F.:* Urol. & Cutan. Rev. **37:** 615, 1933. (21) *Wright, F. R.:* Urol. & Cutan. Rev. **38:** 335, 1933. (22) *Waklin, O. S.:* Svenska LaK-tidning **31:** 137, 1934; Acta dermat.-Venereol. **15:** 243, 1934. (23) *Manwell, E. J.:* New England M. J. **27:** 567, 1934. (24) *Heckel, N. J., Jensen, L. B., and Wood, I. H.:* J. Urol. **33:** 284, 1935. (25) *Cannon, P. R., and Sullivan, F. L.:* Proc. Soc. Exper. Biol. & Med. **29:** 517, 1932. (26) *Culver, Harry:* J. A. M. A. **103:** 637, 1934. (27) *Besredka, A.:* Local Immunization, Baltimore, 1927, Williams and Wilkins Company.

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# HYPOTHYROIDISM AS A PROBLEM IN WOMEN

## A Basal Metabolism Study of 600 Cases

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ABNORMAL development of the thyroid gland, so frequently observed in the so-called goiter areas, presents many interesting medical problems. For centuries physicians have recognized that thyroid hypertrophy in women may occur as a congenital defect, or begin at puberty or during pregnancy. In Charpentier's *Cyclopedia of Obstetrics and Gynecology,* the American edition of which was published in 1887, there is a two-page discussion of goiter and its influence on pregnancy. Under treatment the writer of the article says: "As goiter is generally benign during pregnancy, we should resort to general measures and internal medication. Forbid the patient to nurse and give iodine."

Those of us living in goiter areas formerly accepted a moderate hypertrophy of the thyroid as an incident of pregnancy, and until Marine, in 1917, urged the use of iodine as a preventive measure, most of us who treat women patients gave the thyroid very little thought. Following Marine's advice, in 1920, I began administering iodine in some form to every obstetric patient who showed any hypertrophy of the thyroid. Later it was appreciated that all women living in goiter areas need the

iodine as a protective measure, and every pregnant woman under my care was advised to take it throughout the period of pregnancy. A review of my experience during the first years of this practice indicated that it was a mistake to stop the iodine following delivery, and since 1926 when my first paper on "Thyroid Hypertrophy and Pregnancy" was published, all patients have been advised to continue a reduced dose of iodine indefinitely. During the first years when the iodine was discontinued at delivery, ten patients in a total of 500 delivered returned with classic symptoms of toxic goiter within a year. Since having all patients continue the use of iodine, over 1,000 women have been carried through pregnancy and the puerperium, and to date not one has returned to me with evidence of toxic goiter. However, not all of them have been under periodic observation, and it is possible that such a condition may have been diagnosed elsewhere. Furthermore, not a single congenital hypertrophy of the thyroid has been observed since I have been giving iodine to all pregnant patients. It is evident that the prophylactic administration of iodine to pregnant women is effective in preventing hypertrophy of the thyroid of both mother and fetus. But will the iodine insure a normal development of the thyroid in the fetus of a woman who has hypothyroidism?

The problems associated with underfunction of the thyroid gland were, for many years, overshadowed by hypertrophy of the thyroid and thyrotoxicosis. Gradually it was appreciated that cretinism is not rare in America and that many women have varying degrees of hypothyroidism. DeQuervain, who has had an unusual opportunity to study cretinism, observes that cretins may be divided into two groups: (1) cretins with goiter, and (2) cretinoid dwarfs without goiter, but with an atrophic thyroid gland. He also furnishes evidence obtained by operation that the so-called infantile myxedema, a condition of dysfunction of the thyroid which may be noted first at school age, results from an absence of normal thyroid tissue, in his case there being only a small amount of accessory (sublingual) thyroid tissue which was not very active. The evidence available makes it appear doubtful if the mere administration of iodine to a pregnant woman with a fair degree of hypothyroidism will be sufficient to insure a normal development of the thyroid in the fetus. Many years must elapse before the clinical experiment with iodine, which is being conducted in Switzerland, will permit an answer to this important question. For the present it will be safer to assume that the hypothyroid woman who becomes pregnant should have thyroid medication as well as iodine.

However one may approach the thyroid problem, it becomes evident that control is best accomplished through prenatal care. Thus the real prophylaxis reverts to the physicians who are responsible for the care

of pregnant women. DeQuervain is convinced that the harmful changes which may result from improper development of the thyroid are evident by the seventh month of pregnancy, hence, administration of iodine and, when indicated, desiccated thyroid should be started as early as possible. There is some evidence to suggest that the definitely hypothyroid group should have this medication before the onset of pregnancy. But how are we to tell which women are in the hypothyroid group?

Myxedema, when well developed, should be recognized without difficulty, but most patients with moderate degrees of hypothyroidism do not show definite evidence of thickened skin or fluid retention. However, a considerable number have more or less constantly a slow pulse and a subnormal temperature. It has been our observation that practically all individuals who have the slow pulse and subnormal temperature have a low basal metabolism rate. While this is the best clinical indication that the patient may have a hypothyroidism, there is another group of women who may have an elevated pulse and a normal temperature, yet have a low basal metabolism rate and show marked improvement in their physical condition following the judicious administration of desiccated thyroid. If there is no clinical finding which will enable us to select all of the hypothyroid patients, are we not justified in using metabolism determinations routinely in our examination of women patients?

Preliminary to starting the routine basal metabolism rate in examination of women patients, we made a survey of the findings on all females tested in the laboratory at Columbia Hospital, Milwaukee, for a ten-year period ending Dec. 31, 1931. There were 1,205 women or girls who had one or more basal metabolism rate determinations with the following results:

| | | | |
|---|---|---|---|
| Plus | 55% and up | 36 | |
| Plus | 50-55 | 10 | |
| Plus | 45-50 | 23 | |
| Plus | 40-45 | 13 | |
| Plus | 35-40 | 31 | 410 women or 34% above plus 10. |
| Plus | 30-35 | 23 | |
| Plus | 25-30 | 31 | |
| Plus | 20-25 | 60 | |
| Plus | 15-20 | 95 | |
| Plus | 10-15 | 88 | |
| Plus | 5-10 | 130 | |
| Plus | 0-5 | 110 | |
| | 0 | 21 | 505 women or 42% in normal range. |
| Minus | 1-5 | 134 | |
| Minus | 5-10 | 110 | |
| Minus | 10-15 | 114 | |
| Minus | 15-20 | 77 | |
| Minus | 20-25 | 49 | |
| Minus | 25-30 | 22 | 290 women or 24% below minus 10. |
| Minus | 30-35 | 13 | |
| Minus | 35-40 | 4 | |
| Minus | 40 down | 11 | |

Realizing that a hospital group would include a considerable number of patients who had been sent there with definite symptoms of toxic goiter, the ones whom I had referred to the laboratory for basal metabolism rate determinations were analyzed with the following results: In a total of 172 females with one or more checks there were 34 or 19.8 per cent with a basal metabolism rate above plus ten; a total of 91 or 52.9 per cent within the normal plus or minus ten, and 47 or 27.3 per cent below minus ten. The results of this analysis indicated that a considerable proportion of the women and girls living in Milwaukee and vicinity show abnormal basal metabolic determinations, and I concluded that routine determinations on a considerable series of patients coming to me for examination were justified. In an effort to avoid the criticism that this was adding unnecessary expense to the patient, the necessary laboratory equipment was secured, a competent technician employed, and a routine basal metabolism rate and complete blood count added to my regular general examination without making any additional charge to the patient, the former minimum being maintained. Only after need for repeated examinations had been demonstrated in any case was the cost of the subsequent determinations charged to the patient. The complete blood counts were of definite value, but it has not been possible to observe any relation between the blood count and the basal metabolism rate. The results obtained from routine basal metabolism rate determinations on a consecutive series of 600 females, some of whom have had a large number of tests, are shown in the following table:

| | | | |
|---|---|---|---|
| Plus | 30-35% | 1 | |
| Plus | 25-30 | 5 | |
| Plus | 20-25 | 5 | 48 women or 8% above plus 10. |
| Plus | 15-20 | 14 | |
| Plus | 10-15 | 23 | |
| Plus | 5-10 | 34 | |
| Plus | 1-5 | 46 | |
| | 0 | 14 | 246 women or 41% in normal range. |
| Minus | 1-5 | 58 | |
| Minus | 5-10 | 94 | |
| Minus | 10-15 | 106 | |
| Minus | 15-20 | 98 | |
| Minus | 20-25 | 63 | 306 women or 51% below minus 10. |
| Minus | 25-30 | 31 | |
| Minus | 30-35 | 7 | |
| Minus | 35-40 | 1 | |

A series of 100 pregnant women are included in the above analysis. They were grouped separately, and it was found that 18 per cent had readings above plus ten, 49 per cent within the normal plus or minus ten range, and 33 per cent were below minus ten. It will be noted that this pregnant group average very closely with the 172 patients whom I had tested at Columbia Hospital during the ten-year period.

The data presented indicate that a low basal metabolism rate is relatively common for women living in Milwaukee and vicinity. It is diffi-

cult to determine the percentage of the women with low rates who actually have a hypothyroid condition. The clinical test with the administration of desiccated thyroid is the only method which can be accepted at present, and it is difficult to keep patients under observation for long periods of time unless they are considerably upset from their varied symptoms. Nearly all of the women and girls with rates below minus ten were tested with small doses of desiccated thyroid, and with few exceptions they reported improvement in their general physical conditions and gradual correction of a wide variety of symptoms. A number of those with rates between minus 10 and 15 were found to have a perfectly normal rate after using 100 tablets (⅕ gr. U. S. P.), and as their symptoms were relieved, the medication was discontinued with the instruction that they should return for another basal metabolism rate if further symptoms were noted. A few of these women who have been rechecked were found to have normal rates. On the other hand, it was observed that a goodly number of women showed a lower rate after their nervous condition became stabilized through the use of thyroid.

Interpretation of the basal metabolism rate, like other laboratory tests, may be difficult, except in cases where it confirms clinical findings or furnishes a clew to the thyroid as a factor in the cause of certain symptoms. It is generally recognized that an increased rate is not definite evidence of hyperthyroidism. A decreased rate is a more reliable evidence of thyroid deficiency, but it must always be remembered that this may be a temporary condition secondary to an infection or other cause, and that the thyroid function may be normal when the cause is removed. For this reason thyroid medication should be carefully controlled, even in patients who have evidence of myxedema.

The clinical results obtained following the administration of desiccated thyroid are more spectacular than those noted from most endocrine products. The numbers of patients treated by me do not justify conclusions, but I have found striking evidences of gynecologic problems in women with a low basal metabolism rate. These include uterine hemorrhage, sterility, repeated abortion, and premature labor. Hughes (1934) suggested that miscarriage and malformed babies may be more common in women who have a low basal metabolism rate. Four of the 100 pregnant women included in this study aborted, but only one was in the lower than minus 10 group with minus 14, two were within the normal limits, and one had a rate of plus 15. While this does not indicate any relation between basal metabolism rate and the abortion, during the past ten years I have had several patients with a low basal metabolism rate and had a history of repeated abortions who were able to go through a pregnancy after using thyroid medication. I have observed two women each of whom has delivered two congenitally de-

fective babies, and the only abnormal finding in each instance was a low basal metabolism rate. However, even though they should have normal infants after thyroid medication, we could not prove that the thyroid had made it possible.

A review of the symptoms and physical findings noted on the histories of our 306 patients who had a low basal metabolism rate shows that they have a feeling of fatigue or weakness and drowiness in the majority of cases. In varying degrees they had all of the symptoms noted by Carey (1933) in the group studied in Minneapolis, namely, fatigue, weakness, drowsiness, generalized pains, joint pains, constipation, nervousness (depression, apprehension), menstrual disturbances, sterility, frequent miscarriages, overweight, dry skin, and falling out of hair (occasional). As previously stated, it is evident that women who have a dry skin, subnormal temperature, and slow pulse practically always have a low basal metabolism rate. Very often those who complain of weakness and drowsiness or excessive fatigue without any physical findings suggestive of hypothyroidism have a low rate temporarily, but return to normal after using thyroid medication for some weeks, and thereafter may continue normal for long periods. It is not possible at present to predict the future for this latter group, although one may suspect that as they grow older a considerable number will show other evidence of hypothyroidism.

A comparison of the percentages obtained in this study with earlier observations on pregnant women reported by me in 1926 suggests that there is a marked increase in the number of Milwaukee women who have a low basal metabolism rate. A reduction is also noted in the frequency of hyperthyroidism. Several explanations might be suggested, but they are all hypothetical. Each generation living in a goiter area may be expected to show more evidence of deficiency unless careful prophylactic measures are instituted. The more general use of iodized salt or iodine in other form apparently has reduced the incidence of thyroid hypertrophy and toxic goiter in this area. It is possible that more individuals with deficient thyroids are now passing over to a state of clinical hypothyroidism without first showing evidence of thyrotoxicosis. Certainly this study of 600 women and girls indicates that a low basal metabolism rate is a common condition in the Milwaukee area and justifies including this test in all general examinations. If one-third of all pregnant women in this area do have a low rate, it is evident that a considerable group of infants may show thyroid deficiency within a few years after birth unless the mothers use thyroid medication during pregnancy. It must be admitted that we have no definite proof at present that the use of desiccated thyroid and iodine will enable the woman with a thyroid deficiency to deliver an infant who will have a normal gland, but this medication should increase the percentage of normal infants. Our

present knowledge of the thyroid problem indicates that it must be corrected through adequate medication previous to pregnancy and during the early developmental intrauterine life of the fetus. Therefore, it is evident that prevention of thyroid disease is dependent upon measures which must be instituted by the physicians who care for women during pregnancy.

There is considerable difference of opinion regarding the amount of iodine which should be administered as well as the best means for supplying it. DeQuervain, in 1932, wrote as follows: "The iodized salt dispensed in Switzerland contains so much iodine that its daily use adds 0.5 mg. to the amounts otherwise supplied. This prophylaxis proves efficacious, and is entirely harmless. Occasional untoward reactions are of a transitory nature. But the conclusions drawn from this nation-wide experiment, which is the Swiss iodine prophylaxis, will not be final before a generation treated systematically from mother's womb to the twentieth year of life is subjected to an equally systematic medical control, which will be in about twenty years." He believes that the dose of iodine used in America (2 mg. per day or more) would be dangerous in a region where goiter is endemic, but suggests that larger doses may be used for intrauterine prophylaxis and during childhood. It has been my practice to administer five minims of the syrup of hydriodic acid every other day during pregnancy, or if preferred, an iodostarine tablet three times per week. Following delivery the patient is advised to use iodized salt, and to continue to take the syrup of hydriodic acid or iodostarine each Sunday. As previously stated, over 1,000 patients have been delivered since starting this plan, and not one has returned with any evidence of hyperthyroidism.

If a patient has a low basal metabolism rate, I am accustomed to start with a small dose of desiccated thyroid, varying the amount with the basal metabolism rate, and to increase or decrease the dose according to the subsequent determinations. In every case the smallest dose which will carry the patient is employed. As the dose of thyroid preparations varies, it is important that patients be continued on the product of a single manufacturer. To insure fresh tablets of a uniform material, I have discontinued writing prescriptions for thyroid, and now dispense the tablets just as is done with other gland products which must be administered with the hypodermic. The administration of desiccated thyroid when checked with basal metabolism rate determinations should be free from danger.

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# TOXEMIA OF PREGNANCY

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THERE is but one toxemia during the second and third trimesters of pregnancy. Its clinical manifestations, however, are very numerous; this variety of symptoms is constitutional, therefore dependent upon the individual, and more particularly upon which one of the various systems bears the brunt of the attack, and develops the high lights of the clinical picture.

All toxemic cases can be placed in two great categories, the acute and the chronic. These will be elaborated fully. It may be stated here for emphasis, for further emphasis later, that what the acute case is in symptomatology, the chronic is not; and that in their destructive processes these two differ as greatly as do acute pneumonic infections from chronic infective infiltrations; in fact, the parallel is perfect in most of the particulars.

Acute cases of toxemia have been greatly reduced by the observations of antenatal clinics. But per contra, the chronic cases have not fallen in their incidence, and outnumber the acute cases about fifty to one. Next to finding a specific for toxemia, it must be our chief clinical endeavor to detect the early "larval" stages of the disease. These are usually amenable to treatment. Every mutation of the internal milieu is an accommodation. As a consequence, acute intoxications are dangerous in proportion to their acuteness, because the body cells and their specific functions cannot accommodate themselves to their new environment. Time, and time only, is necessary to permit mutation for accommodation to take place. Hence the relative paucity of eclamptic seizures in chronic cases, and the more prolonged the toxemia, without acute exacerbations, the less is the danger of a cataclysmic discharge.

Blood changes, as elicited by chemical analysis, are the result and not the cause of the toxemia, and are of very little help in the differentiation of those patients who will become chronic nephritics from those in whom there will be no residual diminution of renal capacity. When retention products are chemically recognizable in the blood, the cases are usually easily recognizable clinically as having passed from the stage of "nephrosis" to that of "nephritis."

There are great differences in susceptibility to eclampsia and toxemia, in the age and temperament of patients; and familial factors play an important part.

Our vision as regards the effects of toxemia upon the mother and offspring is too restricted. This is a plea for a long vision study, particularly the study of the child born of a toxic mother, as to its subsequent development to adolescence and maturity. The views of pediatrists differ very widely upon this subject.

Last, this paper will deal in a very cursory way with placental pathology in relation to toxemia. Toxemia and its appended placental pathology is the subject of an exhaustive study which will appear shortly. This paper is a very brief abstract of this monograph. Placental pathology is almost a virgin field and the placenta at term is a veritable museum of abnormal processes. These changes are facts, indisputable, irrefutable; their interpretation into clinical causes is, as yet, chiefly by inference.

## CHARACTERS OF TOXEMIA

Though there is but one toxemia of the late trimesters, one finds that the cases have many clinical manifestations and manifestly, therefore, the proteaneity of the clinical symptomatology must reside within the patient and be constitutional in origin. The clinical picture will depend upon the patient's system that shows the least accommodation to the new toxic environment. The determination of the affected system will depend upon individual instabilities, or low reserve, or specificity in elimination of the poison, or a combination of two or more of these factors. One can readily see how each of these may operate to the detriment of the patient. An unstable nervous or vascular system will show that instability, under the stress of change, incident to a toxic state; the former, in a predisposition to nervous symptoms, and an easy accession to eclampsia; in the latter, to vascular extravasations in the form of edemas, local or general, and hemorrhagic states. Then again, should a large number of kidney tubules and glomeruli have suffered from some antecedent disease and renal reserve consequently be lowered, one can readily understand the establishment of a renal block under the stress of eliminating either a foreign product or a concentrate.

## CLINICAL TYPES OF TOXEMIA

Clinically cases may be divided into acute and chronic. This subdivision, though arbitrary, is extremely useful. It is arbitrary because there are intermediate cases which are neither acute nor chronic; and useful, because the acute and the chronic differ so fundamentally, not only in symptomatology, but also in sequelae, and destructiveness of function, that acute and chronic cases stand to each other in nature of a contrast.

The acute case, like acute lobar pneumonia or any other acute infective invasion, is quickly over, leaving usually a minimal unrecognizable

loss of function after recovery and a reserve capacity that seems, to our imperfect methods of examination, to be unimpaired. But contrast the destructive effect of a chronic lung or other organ infection, its fibrosis, its incidence to the tissue's endeavor to circumscribe the infection, and contrast the consequent loss of functional capacity. The parallel, in this respect, between the acute and chronic toxemias of pregnancy, on the one hand, and that of similar states of infection, is perfect in almost every detail. On the one hand, toxemias, if they do not destroy the patient by virtue of their acuteness, may not impair the patient's powers of procreation in the slightest degree. This is such a common observation that it requires no further elaboration. On the other hand, chronic cases, by virtue of their duration and low intensity, permit a certain corporeal adjustment, an accommodation of cell function to a new internal environment, but function nevertheless, under these new circumstances, means cell stress and that, if prolonged, spells permanent exhaustion and lack of power of recuperation. That state causes decompensation, and therefore *recognizable* pathology, as distinguished from *unrecognized* pathology, which is not apparent because the cells have not fully lost their compensation, and are still operating within their reserve limits. A problem at once presents itself. The popular subdivision of diseases into functional and organic still holds sway, but it has grown very threadbare. The wider science opens the doors into medical dark chambers, the more restricted becomes the number of functional diseases. It is a term used to cover our lack of knowledge. Rather let us realize that functional and organic changes are always synchronous, and that the former are the outward and clinical signs of an inward and organic lack of accommodation to a new environment. Every physical, every chemical change in the human body is an attempt at accommodation and where that accommodation fails, there we have the initiation of the steps that can lead only to extinction of the individual or race.

But just as acute cases leave a minimum of sequelae as contrasted with chronic cases, so are acute cases dangerous by virtue of the suddenness of the changes to which the body has to conform or it must inevitably succumb. So that acute toxemias, like acute infections, are short lived, intense, startling in symptomatology, often destructive of the individual by toxicity, but not destructive of separate systems. Chronic cases, on the other hand, are seldom destructive of the individual by their toxicity, but by system changes and consequent progressive perverted metabolic function. The destructive properties of the chronic cases can be measured by the equation, intensity multiplied by chronicity on the one side, and individual reserve on the other.

Acute cases fall readily into four clinical groups: (1) Renal, (2) hepatic, (3) extravasatory, and (4) neural. These subdivisions have been fully dealt with in my previous papers and require no further

elaboration except that their relative incidence is approximately as follows: 20 renal types to 2 hepatic to 10 extravasatory to 1 neural. The prognosis fortunately is inversely as their incidence. That is, the neural type claims the highest mortality rate, the hepatic next, the hemorrhagic follows, and the renal has the lowest mortality.

### BLOOD CHEMISTRY

The work of studying 300 cases, where blood chemistry was done at least once, or several times during the height of the disease, has proved most enlightening. The variation in blood contents has almost invariably been within normal limits. When, on the other hand, there were evidences of retention in the blood, the cases could usually easily be diagnosed clinically as having passed from a nephrosis to a nephritis. The transition is usually slow and insidious and may not be apparent except under stress. Moreover, it is worthy of our attention that retention products in the blood must not be taken at face value. They are estimable only when taken in conjunction with the patient's history and present condition. The importance of this cannot be overstressed.

There is now in the hospital a woman, sixty-eight years of age. Twenty years ago she had a blood pressure of over 200, taken at several times over a long period. She was told then, after careful clinical and chemical examinations during hospitalization, that she would probably live six months, not more. This was the prognosis of one of the best professors of clinical medicine. She is now under observation with a blood pressure of 240 over 120, and this has never been found below the 200 line at any taking in the past twenty-two years. Her blood chemistry shows an unusually high retention as follows:

Creatinine varies between 4 and 7.36; nonprotein nitrogen varies between 78.4 and 112; urea nitrogen varies between 50 and 81 on repeated examination, and yet the patient is exceptionally well, symptom-free, and capable of doing her ordinary daily round without discomfort.

This case is quoted fully, to illustrate the influence of time in allowing accommodation of cell function to a slowly changing internal milieu. There is probably not any woman who could live with the above quoted chemistry, were the process at all acute, or even subacute. So all values in medicine are relative. The time element is a very weighty factor. It is the time element that determines the differences in symptomatology and the more striking differences in pathology between the acute and the chronic cases.

Another factor to which little or no attention has been given is the individual and familial susceptibility to toxemia and, in particular, to eclampsia. Age is an important factor. In the past eighteen months there have been three cases of eclampsia in girls about sixteen years of age. The seizures were not severe, subsequent coma was short, and the patients were clinically not very toxic. They all recovered without appreciable damage. The percentage of such cases was *very* high as com-

pared with that of older women. The inference is clear that the child's nervous system is more susceptible to nervous explosions than is the more hardened adult. I have had two cases of eclampsia in my own private practice in the past fifteen years. Both of these were morons, veritable children mentally; they both went into convulsions during labor; the convulsions were mild, and short. One had to be transferred to a mental hospital during her puerperium, and has never recovered her normal state of vegetative sanity; the other will probably produce a long list of moronic descendants. This instability and explosive tendency of children is seen clearly in infections, where chills take the place of convulsions. So it is with high strung neurasthenic and hysterical women. They are virtually children in their nervous instability. Time and its thundering impulses have not hardened the nervous system. The alloy is not susceptible to tempering. On the other hand, beware of the woman whose mother has taught her emotional control in her childhood, and who had practiced it in subsequent years. She will not become convulsive until her nervous system becomes saturated, and the union of the toxic agent and the nervous cell may become so intimate as to defy a restoration. If recovery takes place, the nervous sequelae are often severe, distressing, and protracted.

### THE EFFECTS OF TOXEMIA UPON THE OFFSPRING

No one who has seen the effects of chronic toxemia upon the newborn can but be impressed by its seriousness. Since the placenta suffers so much (as will be shown later) from the agents of toxemia, is it natural to assume that the child, of which the placenta is merely an appendage, could be invulnerable? When we consider that all degrees of placental disease, up to the degree of complete sequestration, can occur, is it tenable that the child could escape its effects? Experience teaches us the contrary. If so, then what is the subsequent history of these children? Are they low in system or organ reserve? How do they stand the major diseases of childhood? What is their history as men and women? What is the effect of procreation in women with a history of toxemia in their prenatal life? Pediatricians differ markedly in their reaction to these questions. That is not surprising. It is only in the past few years that this long vision has come into consideration. What is surprising, however, is that one experienced specialist, who has had sad personal experiences, states that they are all below par and most of them die before reaching five years of age. Others equally emphatic minimize the effects of maternal toxemia upon the offspring. The truth, like all truth, is halfway between these extremes. The degree and the duration of the toxemia are factors beyond the ken of the pediatrician, yet these are the dominant factors, and these are known only to the experienced and observing obstetrician. This question of child-effect must demand our most careful and prolonged attention.

PLACENTAL DISEASE

This is almost a new and virgin field of pathology. There issues from its careful study the following diseases, some new, others with a new significance. In the order of their frequency they are: (1) chorionic sclerosis, (2) placentosis, (3) hemorrhages, and (4) degeneration cysts.

Underlying all these, there is a common fundamental cause, toxemia, and a predisposing factor, senility. Every placenta lives the stages of life common to all living things. It has its embryonic period, its childhood, its adolescence, its maturity and its senility. Ordinarily senile predispositions begin about the seventh month. The causes for this were outlined in a previous paper. In other instances senility may be tremendously advanced or somewhat delayed. These are the exceptions. Senility predisposes to a preternatural susceptibility to toxemic changes, just as old age in the individual inflicts a narrowing range of physical and chemical liberty.

Toxemia, on the other hand, is a change in the internal milieu of the pregnant mother, and the acuteness or chronicity of that change determines not only the symptomatology, as previously emphasized, but also the pathology. Acute toxemic states of short duration show a minimum of placental change, only a short-lived, variable placentosis. Chronic toxemic states produce placental changes of a profound character akin to that of chronic inflammatory lesions of the lungs, where all the lesions enumerated above may coexist, in variable degrees, even to the degree of almost complete exclusion of one or more. The insidious extension of any one of these may so impair the function of the placenta as to jeopardize the life of the child. Of chorionic sclerosis and its effect upon restricting the extension of the chorionic plate, I have written fully quite recently. Placentosis, on the other hand, is a new disease. It is acute, or less acute, or chronic. The acute stages are rare and very short lived. The placenta, when so affected, is of a bluish black color, engorged, the fetal vessels are tremendously distended, the cotyledons are swollen and rounded as if under tension. When cut, the placenta oozes almost black blood. When hardened and cut in slices, there are hemorrhages scattered through the placenta, but unless extensive, these are more or less confined to the center of the cotyledons. This is spoken of as the stage of red hepatization, owing to its resemblance to a lung in that pathologic state. Microscopically, the fetal blood vessels are so engorged that their walls are almost invisible, and fetal extravasations of blood are visible in every field. This condition is not a result of labor, for it occurs just as frequently in section cases. This state, if it lasts several days, may lead to complete sequestration of the placenta and, if it be retained a few days, it will be cast off as a huge yellow placenta, in which fatty degeneration is the dominant change.

If, on the other hand, the child should survive, the placenta may undergo complete resolution and leave very few traces of placentosis. If, however, the recovery is slow, it presents a characteristic change. The placenta cuts as, and has the appearance of, a lung under gray hepatization. It cuts in a ragged way after hardening and there is a distinct alveolation, in which the differentiation between cotyledons and maternal intercotyledonous tissue is easily made out. The intercotyledonous tissue is edematous, soft and ragged. The cotyledons are of firmer consistency. The cotyledons recover from the periphery, leaving a central hemorrhage or cavity (alveolation). Placentas may recover in part, other parts may go under sequestration. This will depend upon the site of the placenta and its consequent blood supply. Similarly, in multiple pregnancies, one child may die, while the others may survive. Life depends upon such seemingly insignificant details.

Placentosis in its insidious, more or less chronic, stage may show coincident advances in one area, and imperfect reparation in another. This complicates the picture to a puzzling degree. There is a subtle connection between placentosis and the onset of labor, which will be dealt with in my larger monograph.

Placental hemorrhage is one of the commonest of placental diseases. In the 750 placentas so far examined, there were over 500 cases of macroscopically recognizable hemorrhage. These varied in size from millet seeds to oranges. In only eleven of these was the condition recognized clinically either ante- or intrapartum. It can definitely be established by my studies that this condition is another of the many placental manifestations of a general toxemia. That the placenta is chosen for the baneful changes incidental to toxic states, is in accordance with two distinct biologic factors, first, the law of selectivity, and second, the greater susceptibility of the placenta, because it is a mushroom growth, imperfect in development, short lived, and consequently vulnerable.

Degeneration cysts are found only in the maternal intercotyledonous tissues. They begin as a hyaline swelling and degeneration of the decidual cells very similar to the swelling and hyaline degeneration of uterine tissues postpartum, as described in my monograph upon regeneration of uterine vessels in the puerperium. The centers of these degenerated masses become gelatinized and homogeneous and of a pale green color, or in a less perfect state, the central part contains bizarre phantoms of the swollen cells. The walls are always made up of decidual cells in various stages of degeneration. These cysts are extremely common, affecting about 25 per cent of placentas at full term, and may vary in size from a millet seed to an almond. They have no clinical significance except as an index of degeneration and, when present, they are usually of all sizes and numbers.

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# OVARY-STIMULATING FACTORS AND ANTIHORMONES*

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THE recent discovery that the prolonged administration of gonadotropic hormones to laboratory animals leads to the production of inhibiting substances may prove an important advance in our knowledge of the physiology of sex hormones. It has been recognized for some time[1, 2, 3] that the continued daily injection of laboratory animals with gonadotropic extracts from pregnancy urine or placenta or from anterior pituitary material, leads first to a great increase in the size of the ovaries, but subsequently there results a loss of the gonad-stimulating effect and an actual regression of ovarian weight. It remained for Collip and his collaborators[4, 5, 6] to show that this regression is not due to ovarian failure, because animals injected with chorionic hormone preparations are still able to respond to pituitary extracts and vice versa. For instance, animals given a placental extract (A-P-L) eventually reach a stage where the ovaries not only fail to increase further in size but actually diminish to less than normal weight, and the administration of pituitary preparations at this time still elicits a response. They also noted that the regression of the ovaries of the injected animals is due to the production of certain substances which have the power of completely inhibiting the action of the hormone employed. This can be demonstrated by the fact that extracts mixed in vitro with serum from treated animals become inert, and that a passive resistance can be induced in rats by the injection of such serum. Since this work may possibly find important clinical applications, the present study was conducted to determine some of the properties of such "antihormones" and the conditions under which they may be produced.

## TECHNICAL PROCEDURES

The technical procedures employed in the Stanford Gynecological Laboratory and details regarding the animals, their age at maturity, the method of estimating organ weights and their percentage of increases, and the standardized way in which the extracts are administered, have been fully described in a number of previous communications.[7, 8, 9, 10, 11] In experiments of long duration control

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figures for organ weights were obtained for this study from groups of seven or more normal rats sacrificed at 51, 82, 111, and 141 days of age. The method of preparation of ovary-stimulating extracts from blood of pregnant women has also been given before.[7, 10] It is based on the work of Wallen-Lawrence and van Dyke,[12] and depends on an alcohol precipitation of citrated blood, extraction of the precipitate with a sodium-acetate-acetic acid buffer, pH 4.2 to 4.5, and reprecipitation of the active material with 95 per cent ethyl alcohol. The human anterior lobe extracts were prepared from autopsy material obtained from patients of both sexes and of all ages. The fresh glands were cut into small fragments and kept in acetone for several days or weeks, and were finally dried in vacuo at room temperature. They were then ground up, and the resultant powder extracted in the same way as that used for making extracts from blood of pregnant women.

The method of testing for the "antihormone" property of the serums of injected animals was similar to that first employed by Collip and Anderson[13] in studying the antithyrotropic hormone. A mixture of equal amounts of serum and one of the extracts was injected into groups of immature rats. It was given twice daily in 0.5 c.c. doses for four days, and the rats were sacrificed in 120 hours. The potency of the extracts used is not given in rat units but was determined by injecting control series of rats with a mixture of the same preparation and an equal amount of serum from normal animals. It was thus possible to compare directly the effects induced in 120 hours in the ovaries of immature rats.

## RESULTS

*Human Pituitary Extract.*—The first series of experiments consisted in the daily injection of a small dose of human pituitary gonadotropic extract to immature rats 21 to 23 days of age. A total of 39 animals was used for this purpose, and the injections were continued for as long as 119 days. Seventeen rats were autopsied in 5 days, while 6 were sacrificed in 30 days, 6 in 61 days, 6 in 90 days, and 10 in 119 days. In addition, 20 rats were treated for 119 days, and were then injected for 5 days with either sheep pituitary extract or pregnancy blood extract.

The effect of such injections on ovarian weight is shown in Fig. 1. In 5 days the ovaries had increased 50 per cent over the weight of the control animals, and in 30 days the increase was 86 per cent, but after treatment for 61 days, the ovarian weight was equal to that of the controls, while in 90 and 119 days it had actually diminished 26 and 19 per cent.

The serum of the rats injected for 90 and 119 days was examined in the manner described in the preceding section for the presence of any "antihormones." As shown in Table I, it was found to possess a great inhibiting power toward extracts prepared from human pituitary gland material. For instance, Extract 55 mixed with an equal amount of serum from normal animals was able to induce a 618 per cent increase in ovarian weight of immature rats over a five-day period. On the other hand, the ovaries of young rats injected in the same manner and with the same extract but mixed with serum from animals treated previously for 90 days, failed to show any response and actually weighed 10 per cent less than those of normal controls.

In contrast to the definite "antihormone" property of this serum as regards human pituitary extracts, it was now found that it was unable to inhibit the action of preparations made in the same way from sheep hypophyses. A mixture

of sheep pituitary extract and the serum from the injected rats produced an increase in ovarian weight of 300 per cent, whereas the same extract mixed with normal rat serum resulted in a 210 per cent increase.

A remarkable finding, however, was the fact that the serum of the rats injected for long periods of time with human pituitary extract had "antihormone" properties toward the chorionic gonadotropic hormone. A mixture of normal rat serum and pregnancy blood gonadotropic Extract 26 was able in five days to cause a 190 per cent increase in ovarian weight, and histologic examination showed the presence of corpora lutea, lutein cysts, and developing follicles. On the other hand, the same extract mixed with an equal amount of serum from the experimental rats induced no increase in the weight of the ovaries which histologically gave the picture seen in normal immature rats.

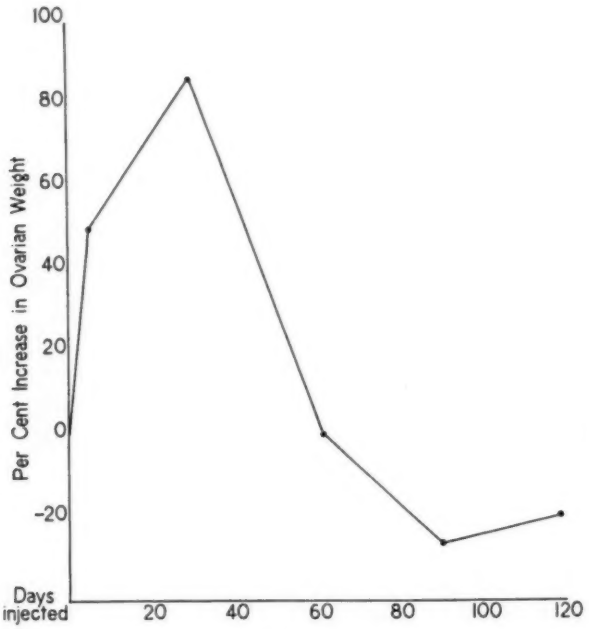


Fig. 1.

Since the ovaries of rats injected for 119 days with a human pituitary extract weighed less than those of normal controls, it seemed of importance to repeat the experiment of Selye and others[4] and determine whether they could still respond to other preparations. Ten rats treated in this way thus received two injections daily of a sheep pituitary extract and were sacrificed in five days. It was seen that the ovaries were still capable of responding and showed a 61 per cent increase in weight. A second series of 10 similar rats were given two daily injections of a pregnancy blood extract, but in five days the ovaries showed only a slight increase (23 per cent). The blood serum of the rats used in these experiments also showed the presence of "antihormones" effective against human pituitary and pregnancy blood extracts.

*Chorionic Gonadotropic Hormone.*—The injection of pregnancy blood extract to rats over a long period of time in order to stimulate the formation of antihormone has met with a number of technical difficulties. These experiments are

therefore incomplete and must be reported at a later date. However, in keeping with the work of Twombly and Ferguson[14] and Bachman, Collip and Selye,[15] it has been found that inhibiting substances readily form in the rabbit.

Two rabbits were injected once daily with a gonadotropic pregnancy blood extract for periods of forty-two and seventy-four days, respectively. At the end of that time the animals were sacrificed and the blood serum examined for the presence of antihormones.

TABLE I. THE DEMONSTRATION OF ANTIHORMONE PROPERTIES IN THE BLOOD SERUM OF RATS INJECTED FOR A LONG PERIOD OF TIME WITH A HUMAN PITUITARY GONADOTROPIC EXTRACT

| | NUMBER OF RATS | AVERAGE BODY WT. | GROSS WEIGHTS | | PER CENT INCREASE OVARIAN WEIGHT |
|---|---|---|---|---|---|
| | | | UTERUS | OVARIES | |
| H.P.E.* No. 55 plus N | 3 | 28 | 0.072 | 0.082 | 618 |
| H.P.E. No. 55 plus H | 4 | 42 | 0.029 | 0.013 | –10 |
| H.P.E. No. 57 plus N | 4 | 29 | 0.055 | 0.026 | 118 |
| H.P.E. No. 57 plus H | 4 | 28 | 0.063 | 0.009 | –23 |
| S.P.E. No. 50 plus N | 5 | 35 | 0.053 | 0.037 | 210 |
| S.P.E. No. 50 plus H | 5 | 39 | 0.059 | 0.052 | 300 |
| P.B.E. No. 25 plus N | 5 | 27 | 0.103 | 0.020 | 72 |
| P.B.E. No. 25 plus H | 4 | 39 | 0.081 | 0.010 | –20 |
| P.B.E. No. 26 plus N | 4 | 37 | 0.136 | 0.038 | 190 |
| P.B.E. No. 26 plus H | 4 | 43 | 0.035 | 0.015 | 0 |

*H, Serum from rats injected daily with a human pituitary extract for 90 or 119 days.
N, Serum from normal control rats.
H.P.E., Human pituitary extract.
S.P.E., Sheep pituitary extract.
P.B.E., Pregnancy blood gonadotropic extract.

As shown in Table II, the serum from the injected rabbits was able to render pregnancy blood extracts ineffective. Pregnancy blood Extract 313 mixed with serum from a normal rabbit induced a 155 per cent increase in the weight of the ovaries of immature rats, while the same preparation mixed with serum from the animal injected 74 days gave only a 40 per cent increase.

On the other hand, the serum was unable to inhibit extracts prepared from either human or sheep pituitary glands. The "antihormone" property developed by the rabbit serum was thus effective only against the chorionic gonadotropic hormone.

*Blood of Postpartum Patients.*—During pregnancy in the human being, there is a constant production and excretion of a very active gonadotropic substance which is readily demonstrable in the blood and urine but which rapidly disappears after delivery. Since Bachman and his collaborators[15] have shown that antihormones may persist for a long time after the cessation of treatments in experimental animals, it seemed that the puerperal woman presented a unique opportunity to determine if inhibiting substances are formed under the stimulus of a hormone produced by an individual in physiologic conditions.

The blood of four patients from five to nine days postpartum was first examined and found to be free of chorionic gonadotropic factors. It was then

mixed in equal amounts with a pregnancy blood extract or with a human pituitary gland preparation and tested for the presence of antihormones as in the

TABLE II. THE DEMONSTRATION OF ANTIHORMONE PROPERTIES IN THE BLOOD SERUM OF RABBITS INJECTED FOR A LONG PERIOD OF TIME WITH A PREGNANCY BLOOD GONADOTROPIC EXTRACT

| | NUMBER OF RATS | AVERAGE BODY WT. | GROSS WEIGHTS | | PER CENT INCREASE OVARIAN WEIGHT |
|---|---|---|---|---|---|
| | | | UTERUS | OVARIES | |
| H.P.E.* No. 64 plus N | 3 | 41 | 0.104 | 0.089 | 540 |
| H.P.E. No. 64 plus R | 3 | 20 | 0.090 | 0.049 | 427 |
| S.P.E. No. 70 plus N | 3 | 24 | 0.064 | 0.041 | 340 |
| S.P.E. No. 70 plus R | 2 | 30 | 0.067 | 0.095 | 682 |
| P.B.E. No. 31 plus N | 3 | 29 | 0.114 | 0.025 | 190 |
| P.B.E. No. 31 plus R | 3 | 25 | 0.076 | 0.015 | 30 |
| P.B.E. No. 313 plus N | 3 | 27 | 0.086 | 0.031 | 155 |
| P.B.E. No. 313 plus R | 3 | 34 | 0.024 | 0.016 | 40 |

*R, Serum from rabbit injected for 74 days with a pregnancy blood gonadotropic extract.
N, Serum from normal control rabbits.
H.P.E., Human pituitary extract.
S.P.E., Sheep pituitary extract.
P.B.E., Pregnancy blood gonadotropic extract.

previous experiments. In no instance could these be demonstrated by this means, and it would thus seem that inhibiting substances do not form in the pregnant woman in spite of the constant excessive production of the chorionic gonadotropic factors for the whole duration of gestation.

## COMMENT

The experiments reported in this study corroborate the finding of Collip and his collaborators that the prolonged administration of gonadotropic extracts leads to the production of substances capable of inhibiting the action of similar preparations. There is, however, a definite species-specificity as regards the formation of these substances, and it is as yet uncertain whether definite "antihormones" are formed or whether the inhibition can be attributed to an immunologic reaction.

From the standpoint of the clinician, two observations are worthy of note. In the first place, it is yet uncertain that "antigonadotropic hormones" will prove of great importance in the study of various pathologic conditions associated with menstrual disorders. At any rate, it will first be necessary to demonstrate that they may be produced under the stimulus of hormones normally present in an individual. Second, the formation of such substances in experimental animals requires a prolonged course of treatment. It seems doubtful, therefore, that the present clinical usage of active gonadotropic extracts could lead to the same result, although this problem is open to experimental investigation.

SUMMARY

A series of experiments has been conducted to study the occurrence of "antihormones" in the blood of experimental animals injected daily for a long period of time with gonadotropic extracts.

The injection into rats of a preparation of human pituitary gland for 90 or 119 days resulted in the production of substances capable of inhibiting the action of gonadotropic extracts prepared from both human hypophyses and from blood of pregnant women. A species-specificity was demonstrable, however, as it proved ineffective with sheep pituitary extracts.

The administration to rabbits of a human pregnancy blood gonadotropic extract for seventy-four days resulted in the production of substances capable of inhibiting similar extracts, but ineffective against either human or sheep pituitary gland preparations.

It was not possible by similar means to demonstrate any "antihormones" in the blood of women during the first ten days of the puerperium.

REFERENCES

(1) *Zondek, B.:* Die Hormone des Ovariums und des Hypophysenvorderlappens, Berlin, 1931, Julius Springer. (2) *Collip, J. B.:* Internat. Clin. **4:** 51, 1932. (3) *McPhail, M. K.;* J. Physiol. **80:** 105, 1933. (4) *Selye, H., Collip, J. B., and Thomson, D. L.:* Proc. Soc. Exper. Biol. & Med. **31:** 487, 1934. (5) *Idem:* **31:** 566, 1934. (6) *Collip, J. B.:* J. Mt. Sinai Hosp. **1:** 28, 1934. (7) *Fluhmann, C. F.:* Proc. Soc. Exper. Biol. & Med. **29:** 1193, 1932. (8) *Idem:* **30:** 147, 1932. (9) *Idem:* **30: 881, 1933.** (10) *Idem:* **Endocrinology 17: 550, 1933.** (11) *Idem:* Am. J. Physiol. **106:** 238, 1933. (12) *Wallen-Lawrence, Z., and van Dyke, H. B.:* J. Pharmacol. & Exper. Therap. **43: 93, 1931.** (13) *Collip, J. B., and Anderson, E. M.:* Lancet, p. 76, 1934. (14) *Twombly, G. H., and Ferguson, R. S.:* Proc. Soc. Exper. Biol. & Med. **32:** 69, 1934. (15) *Bachman, C., Collip, J. B., and Selye, H.:* Ibid. **32: 544, 1934.**

STANFORD UNIVERSITY HOSPITAL

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**Puhr, L.: The Pathogenesis of Krukenberg Tumors,** Monatschr. f. Geburtsh. u. Gynäk. **99:** 229, 1935.

The author emphasizes the rarity of Krukenberg tumors. During the last seventeen years only three cases were encountered in the Second Woman's Clinic at Budapest. He reports a case where the lesions were limited to the mucous membranes, chiefly those of the bronchi, stomach, gallbladder, common duct and the urethra. However, other organs were infiltrated, including the ovaries, liver, lungs, adrenals, lymph glands and bones.

J. P. GREENHILL.

# RECENT ADVANCES IN HYSTEROGRAPHY

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MOST of the previous roentgen studies of the uterus have been made during the course of investigations for tubal patency. This has been done, for the greater part, with iodized oils which have yielded very satisfactory shadows, indicating the size, shape, and tonicity of the uterus. Sometimes intrauterine lesions were demonstrated. The method, therefore, was extended to the investigation of the uterus itself. However, on complete filling of the cavity with contrast material, the density of the medium was so great that small lesions were often obscured or the irregularities of contour obliterated by the pressure employed. Some technical difficulties were occasionally experienced in keeping the medium in the uterus while changing the patient's position. Also, there were certain dangers attending its use when recent bleeding had occurred. Last year we reported the development of a contrast medium for the roentgen demonstration of the relief of the endometrium.

A thorium hydroxide solution has been used for this purpose. On contact with alkaline mucus the solution is converted to a gel which adheres to the surface, thus applying a radiopaque coating.

We have used the following technic: The patient is placed in stirrups. After soap and water preparation, a bimanual examination is made to rule out pregnancy and active pelvic inflammatory disease. A large bivalve speculum is inserted, the cervix cleansed with alcohol, and the posterior lip grasped with a tenaculum. Two or three small graduated dilators are passed, dilating the cervix sufficiently to insure a free return of fluid around the cannula. About 20 c.c. of the medium are slowly injected into the uterine cavity allowing the excess to run back into the vagina as injection proceeds. The cannula is then removed and the remaining material wiped from the vault with gauze. It is advantageous to leave the coagulum adhering to the portio. The speculum is removed leaving the tenaculum in place and the patient transferred to the radiologic table. One anteroposterior film is taken on the Potter-Bucky diaphragm and developed at once. A sufficient quantity of contrast material usually adheres to the endometrium to cast a satisfactory shadow on the film. Occasionally the shadow is too faint and the injection must be repeated; or too dense, in which case expulsion of the excess can be promoted by allowing the patient to walk about for a few minutes. If the film is satisfactory, right and left oblique and posteroanterior exposures are made.

The roentgenograms constitute a record of the surface markings of the endometrium and show a considerable amount of detail previously unobtainable.

Examination of a normal uterus in this manner shows:

1. The contour of the uterine cavity.

2. The surface markings of the endometrium. These produce a mottled or finely latticed appearance when the examination is made shortly after menstruation. As the cycle progresses the markings become coarse and the endometrium is thrown into longitudinal folds.

3. The cervical canal. The longitudinal folds may extend into it for a variable distance. It is normally smooth and regular in outline.

4. The portio frequently shows on the plates.

Certain pitfalls have been encountered during the course of our work which may lead to errors in or interfere with the radiologic diagnosis. We have previously warned against the introduction of air. An air bubble can produce a clear rounded shadow similar to a polyp. Atten-

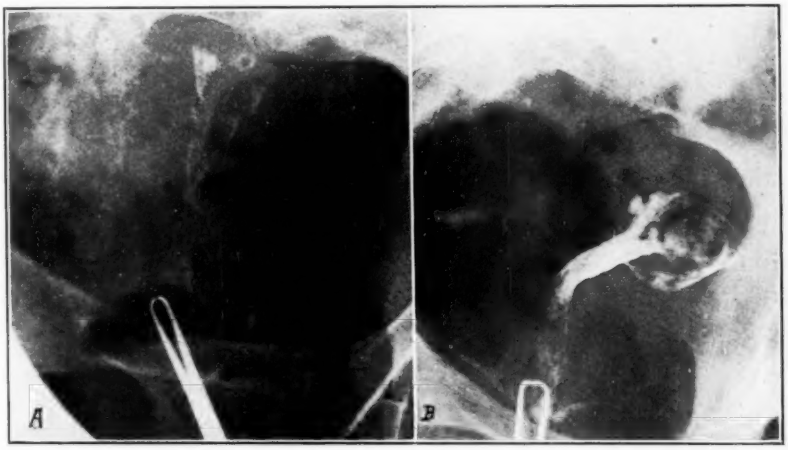
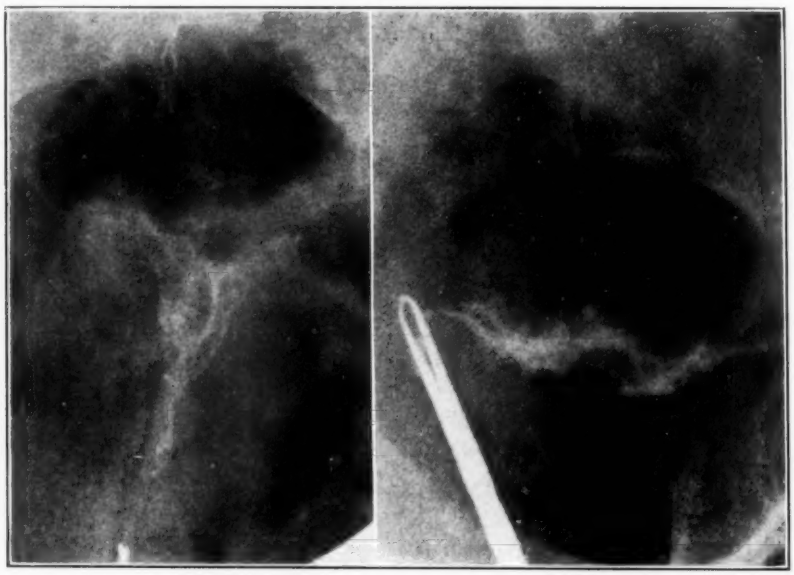



Fig. 1.—*A*, Hysterogram showing small polyp in the fundus. *B*, Small fibroid protruding into the fundus resembling a large polyp.

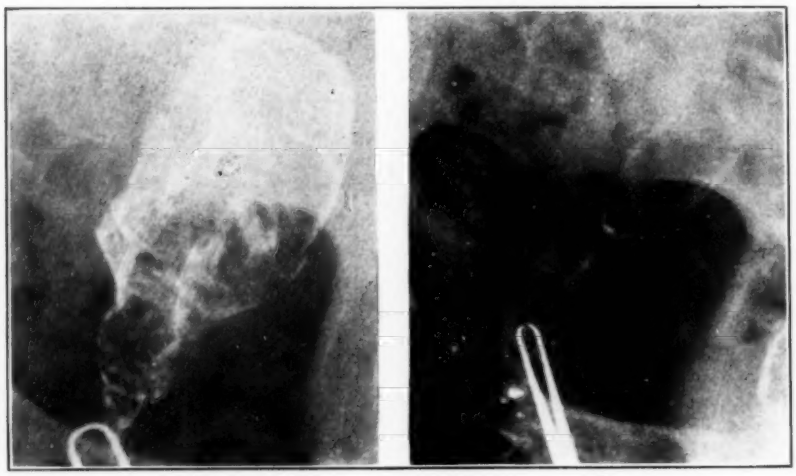
tion has also been called to the necessity of a free return of the excess fluid around the cannula in order to prevent, if possible, the passage of solution through the tubes. We have seen no serious effects from spill into the peritoneal cavity, but confusing shadows are produced by deposit of the material outside of the uterus and tubes which make the plates unsatisfactory for diagnosis. Contrast material in the tubes does not usually interfere with the study. In one case with retrodisplaced uterus, it did cause confusing shadows. The material deposited in this manner remained in the tubes for three weeks. It was our impression that we had demonstrated a hydrosalpinx. Examination of the specimen removed at operation showed this to be an endometriosis of the tubes. The presence of opaque material in the gastrointestinal tract may prevent a satisfactory examination. One such case occurred in which the defect produced by the bulging of a fibroid into the uterine cavity, as

well as an irregularity of the surface immediately below that point, caused by an early carcinoma, were obscured on all but one plate by the presence of a bismuth mixture in the colon. Satisfactory examination of the latter area is quite impossible on this account.



*A.* *B.*

Fig. 2.—*A*, Hyperplasia. Note regularity of uterine contour. *B*, Advanced malignancy (adenocarcinoma). Note irregularity of shadow.



*A.* *B.*

Fig. 3.—*A*, Uterine fibroid. Examination on account of profuse bleeding. *B*, Hysterogram of same case six months following radium treatment. Patient symptom free.

In case of large pelvic tumors we have found the method useful in differentiating between those displacing the uterus and those involving it. The former are characterized by the presence of a uterine shadow

of normal size and shape in an abnormal position. The latter show varying degrees of distortion of the uterine cavity.

The examination of cases in which intrauterine lesions were suspected has yielded much interesting information. Hyperplasia has been diag-

*A.* *B.*

Fig. 4.—*A*, Malignancy in cornu of uterus (adenocarcinoma). *B*, Demonstration of radium application; radium tube held in the involved cornu close to the lesion.

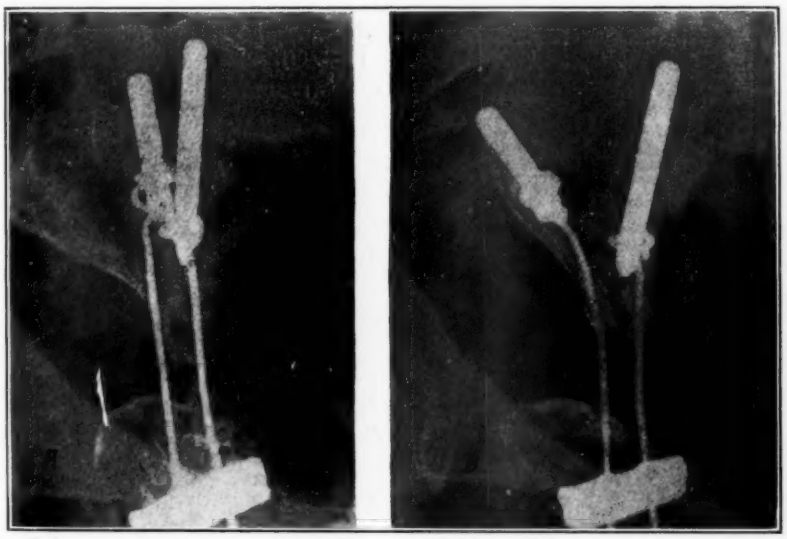


Fig. 5.—*A*, Demonstration of unsuccessful attempt to place one radium tube in each cornu. *B*, Good application of radium showing tubes in proper position.

nosed by extreme enlargement of the folds without loss of smooth outline. With the broadening of the folds there is a corresponding decrease in their number.

Frequently small polypoid elevations are shown on such films in the form of tiny, smoothly rounded shadows. Larger polyps have been located in other cases. They are characterized by clear circular shadows surrounded by rings of contrast material. If the base of the polyp is broad it may be caught in profile on some of the films.

Small submucous fibroids, if protruding far into the uterine cavity, may produce the same type of shadow. The indentation caused by protrusion of most submucous fibroids is sharply defined and with smooth margins. The endometrium is stretched and shows a few faint markings over the lesion. Larger fibroids show marked deformity of the cavity on the films.

Some cases (of fibroids) have been examined six months after radium treatment. Marked shrinking of the lesion has been shown with decrease in size of the cavity and atrophy of the endometrium. On account of the unusually smooth surface and the diminished production of mucus, very little contrast material will adhere to the surface and the shadows are faint.

Other defects in the shadow of the corpus have been detected. They do not produce the clean-cut margins characteristic of fibroids. Endometrioma has been found and masses of retained products located. In case of small flat lesions, like the former, we feel that radiologic diagnosis alone is not safe and that immediate biopsy is indicated. In the latter instance the ovoid shape of the cavity is the clue to diagnosis.

Carcinoma produces irregularity in the uterine outline. In the cervical canal the early lesion exhibits only a localized narrowing and slight irregularity. Occasionally a small crater can be demonstrated. In more advanced lesions the shadows may be broader, the margins more irregular and deep ulceration shown by flecks of material which have penetrated into the small crevices. The margins of the lesion are frequently elevated.

By defining the local limits of the lesion and its depth of ulceration, we have felt that the quantity and distribution of radium could be more accurately gauged. The proper application of the radium tubes can be accurately demonstrated by injecting immediately before or after radium insertion. The outline of cervix and corpus can be shown, the limits of the local lesion defined, and the relation of the radium tubes to the lesion demonstrated.

In the body of the uterus, carcinoma produces only slight irregularity of outline in its early stages. Crater formation has been shown in the region of the internal os. Advanced lesions produce increasing irregularity with evidence of erosion. Radium application is more difficult without plates for control as the radium might easily be placed far from the lesion in the enlarged fundus. This point is well illustrated by the following case:

Mrs. C. D., aged fifty years, gave a history of irregular bleeding for eighteen months. She had passed the climacteric seven years previously. The hysterogram showed a large irregular defect of the fundus. Biopsy from this area proved the diagnosis of adenocarcinoma. This patient was a poor operative risk and radium treatment was selected as the method of choice. A 50 mg. tube of radium attached to an empty tube to hold it in position in the fundus was inserted into the uterine cavity and the lower tube fixed to the cervix with a clip. Fortunately it passed into its proper position close to the lesion. Treatment was given in this manner for 600 mg. hours. After a twenty-four-hour rest, two tubes, each containing 50 mg., were fastened to wire applicators and inserted at angles designed to pass one into each cornu. A check of the placement showed both tubes in the same cornu, the second one slightly lower than the first inserted. The second tube, therefore, was removed, the applicator wire bent to a different angle and inserted in proper position. Both were fastened by a lead clip at the cervix. It is easy to understand how the radium might all be placed more than 2 cm. from the lesion in cases similar to this and the greater part of the benefit of treatment lost. This may explain some of the poor results obtained from irradiation of lesions in the fundus.

SUMMARY

1. A recent method of hysterography has been described which permits the demonstration of the surface markings of the endometrium.

2. Findings on investigation of cases of uterine bleeding have been described. The results have been checked by biopsy or by gross and microscopic examination.

3. Some results of irradiation have been shown.

4. A technic for demonstrating the control and accuracy of radium placement has been discussed.

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**Quénu J., and Béclère, C.: Metrorrhagia in Young Women and Curettage,** Bull. Soc. d'Obst. et de Gynéc. **23**: 686, 1934.

The authors curetted 30 young women for metrorrhagia. In 21 per cent of the cases as definite causes for the excessive bleeding were discovered: cancer of the body of the uterus, small submucous fibroids, polyps, and dermoid cysts. In 78 per cent of the cases no histologic lesions could be demonstrated. However, in more than half of these cases there existed a chronic infection of the genitalia most likely responsible for the bleeding. In not a single instance did curettement lead to any complication.

A follow-up after seven years showed that five patients had to have further operations because the bleeding returned. Four were operated upon and one was treated by roentgen ray therapy. In five more patients irregular bleeding recurred but apparently no further treatments were given. In two women the profuse bleeding ceased but abdominal pains persisted. Only in seven women did the menstrual periods become regular and normal. Four of these patients subsequently became pregnant. This means that 50 per cent of the patients had recurrences. Therefore, curettement alone is not a satisfactory treatment.

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# WHEN IS SURGERY INDICATED IN RETRODISPLACEMENT OF THE UTERUS?

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THE material for this paper has been accumulated from a review of the histories of 145 women with retrodisplacement on whom Dr. Arthur H. Curtis or I have operated during the past five years. These cases have been gleaned from a large number of women with retrodisplacement and represent the group in whom surgical intervention appeared necessary. However, I have not determined the percentage of retrodisplacements which require surgical correction. In this paper, "retrodisplacement" means *marked* retrodisplacement, usually of a heavy uterus.

## CLASSIFICATION OF CASES

An attempt was first made to determine the importance of the retrodisplacement per se in the production of symptoms; this proved to be a difficult task. In some instances the displacement was obviously responsible for symptoms—these I have termed *essential* displacements; in others it was equally apparent that associated lesions were of chief importance—such cases will be called *incidental* displacements. Many times it was almost impossible to decide whether the uterine displacement or the associated pathology was of greater importance, and the following factors have been considered before classifying these cases either as essential or incidental displacements:

1. Age and social status of the patient
2. Character, time of onset, and severity of symptoms
3. Indications for surgical intervention
4. Type and extent of associated pathology encountered at operation

In 83 (57 per cent), the retrodisplacement seemed to be the essential lesion, and in 62, or 43 per cent, it was apparently only an incidental feature of more important associated pelvic pathology.

## ASSOCIATED PELVIC PATHOLOGY

Practically all, in fact 94 per cent, of these patients presented some associated genital pathology; in only 6 per cent was retrodisplacement the sole abnormal finding at operation. At once a rather pertinent ques-

tion arises: Are the symptoms, from which these women sought relief, due primarily to the displacement or are they caused by associated pathology? In many cases it is certain that the associated genital lesions were of little importance.

Among the 83 which I have termed *essential* retrodisplacements, there were 9 with no associated pathology (but only 1 was nulliparous); 19 presented childbirth injuries which also required surgical correction; 11 had endometriosis; there were 10 with cervicitis and leucorrhea which necessitated cauterization or amputation of the cervix; 8 had residues of pelvic infection; 7 had uterine fibroids; 5 had small ovarian cysts; 5 had painful postoperative adhesions; 5 had appendicitis; 2 had both fibroids and endometriosis; 1 had a fist-sized parovarian cyst; and 1 had a localized adenomyoma of the uterus.

Of the 62 patients with *incidental* displacement, there were 12 with residues of pelvic infection and 11 with symptom-producing childbirth injuries, such as prolapse, procidentia, rectocele, and cystocele; 8 were complicated by extensive pelvic endometriosis; 8 were older women, at the menopause, whose sole complaint was bleeding; 5 had appendicitis and the correction of the displacement was largely a prophylactic measure; 4 were operated upon chiefly to relieve adhesion pain; 4 had childbirth injuries with associated endometriosis; 3 had uterine fibroids; 2 had large ovarian cysts; 2 had both fibroids and endometriosis; 1 had both childbirth injuries and fibroids; 1 had an ectopic pregnancy; and 1 had tuberculous salpingitis.

### AGE

Most of our patients were young women; their average age was 32.4 years. The average age in the essential displacement group was 30 years; in the incidental series, it was 35.5 years.

### MARITAL STATUS

There were 20 unmarried women whose average age was twenty-eight years, and 125 married women averaging 33.1 years. Twelve of the unmarried are classified as essential displacements and 8 as incidental; in other words, about 13 per cent of each group were unmarried nulliparous women and 87 per cent were married.

### SYMPTOMS

The most frequent symptoms were (1) lower abdominal discomfort, (2) uterine bleeding, (3) dysmenorrhea, (4) sterility, and (5) backache.

1. *Lower Abdominal Discomfort.*—A bearing-down sensation, with a feeling of weight and heaviness in the lower abdomen and pelvis, occurred in 68, or 47 per cent, of the patients. Forty-four (30 per cent) suffered from an almost constant

lower abdominal ache, often exaggerated during menstruation. In 18 there was no complaint of abdominal pain; in 10, it was definitely appendix distress and in 5, the pain resulted from postoperative adhesions.

2. *Uterine Bleeding.*—Ninety-four, or 65 per cent, of the patients had abnormal uterine bleeding, and in 51 there was no deviation from the normal.

In 25 patients the periods were prolonged and profuse; in 23 the loss of blood was excessive; 15 menstruated too frequently, flowed too long and bled excessively; in 8 the periods were prolonged (ten days or longer); in 8, bleeding occurred too frequently, every week or two; in 8, there had been continuous uterine bleeding for weeks; and in 7 there was intermenstrual spotting which sometimes tended to appear about the middle of the menstrual cycle.

Of the 51 women who gave histories of normal menstruation, 29 are classified as essential displacements and 22 as incidental. In other words, 35 per cent of each group menstruated normally although bleeding was one of the indications for operation in 65 per cent of the patients.

3. *Dysmenorrhea.*—In 63 patients (44 per cent), there was insufficient menstrual pain to call it a complaint; 37 (26 per cent) had acquired dysmenorrhea during adult life; 29 had always had crampy discomfort; 14 complained of a bearing-down discomfort; and in 2 the chief discomfort was pain in the appendix region.

Of the 37 complaints of *acquired* dysmenorrhea, 16 occurred in essential displacements and 21 in the incidental group. In other words, 19 per cent of the essential cases acquired an intense dysmenorrhea during adult life, while it appeared in 34 per cent of the incidental displacements. There were 14 cases each, of essential and incidental displacement, who showed endometriosis and adenomyosis. Five of the 14 essentials, or 36 per cent, complained of acquired dysmenorrhea, but it occurred in 11 or 79 per cent of the incidental displacements with endometriosis, again emphasizing the importance of acquired dysmenorrhea as a symptom of pelvic endometriosis.

4. *Sterility.*—Among the 19 married women who complained of sterility, 9 had extensive pelvic endometriosis; in 3, it was found that the tubes had been removed at a previous operation; 2 had uterine fibroids; 1, the residues of a gonorrheal infection with occluded tubes; 1, the residues of a postabortive infection with phimosis of the fimbriated ends of the tubes; another, tuberculous salpingitis; in another, the ovaries were unusually large, cystic and edematous, a three-inch, right-sided, parovarian cyst was present, the cervix was inflamed and was the source of an annoying leucorrhea; in another, the only associated pathology was a three-inch corpus luteum hematoma. Retrodisplacement, per se, was not responsible for the sterility of these women.

5. *Backache.*—Eighty-one (56 per cent) patients did not complain of backache; in 19 the character and site of the pain was not described; in 18 or 12 per cent it was said to be in the low back, often a dragging ache accentuated at menstrual times and in some instances relieved by wearing a pessary; in 17 the ache was located in the lumbar region; 5 patients were known arthritics; and in 5 there was sacroiliac disease. Consequently the retrodisplacement could not have been responsible for backache in more than one-fourth of our patients.

It is usually possible to differentiate an orthopedic backache from one of genital origin. This is best accomplished by a carefully elicited history and a complete physical examination with accurate localization of the site of the pain, also through attempts to reproduce or accentuate the backache by making traction on the uterus, especially on the uterosacral ligaments, or to relieve it with an appropriate pessary. Such procedures permit the examiner to predict before

operation whether relief from the backache will follow correction of obvious genital pathology. *Not a single patient was operated upon solely for the relief of backache.*

6. *Miscarriages.*—Seventy-six or 61 per cent of the married women had had no miscarriages and 34 or 27 per cent had had 53 spontaneous miscarriages. However, there had been 238 full-term pregnancies, consequently the incidence of spontaneous miscarriage was only 18 per cent; for the state of Illinois it is estimated to be 20 per cent. *None of the patients of this series came to operation because of a tendency to abort repeatedly.*

## INDICATIONS FOR SURGICAL INTERVENTION

The four chief complaints, viz., lower abdominal discomfort, bleeding, dysmenorrhea, and sterility, were grouped as symptoms and constituted the indications for operation as follows:

| | |
|---|---|
| 1. Lower abdominal discomfort, dysmenorrhea and bleeding | 43 cases |
| 2. Lower abdominal discomfort and bleeding | 27 cases |
| 3. Lower abdominal discomfort and dysmenorrhea | 21 cases |
| 4. Lower abdominal discomfort | 21 cases |
| 5. Bleeding | 8 cases |
| 6. Lower abdominal discomfort, dysmenorrhea, bleeding and sterility | 7 cases |
| 7. Bleeding and dysmenorrhea | 6 cases |
| 8. Lower abdominal discomfort, dysmenorrhea and sterility | 4 cases |
| 9. Sterility | 3 cases |
| 10. Lower abdominal discomfort, bleeding, and sterility | 2 cases |
| 11. Lower abdominal discomfort and sterility | 2 cases |
| 12. Dysmenorrhea, bleeding, and sterility | 1 case |

## OPERATIVE PROCEDURES

*Types.*—The operations have been divided, according to the manner of approaching the uterus, into 124 *abdominal* and 21 *vaginal* procedures. Preservation or forfeiting of the childbearing function has permitted a further division into *reconstructive* and *destructive* operations, respectively.

*Abdominal Reconstructive Operations.*—The classical abdominal replacement operation which we have employed most frequently utilizes all supporting structures in maintaining the uterus in an anterior position; at the same time it preserves the normal mobility of the uterus. This operation consists of three separate steps: First, suturing together the relaxed uterosacral ligaments with silk for a distance of 1½ to 2½ inches below their cervical insertion in conjunction with silk suturing of the lax posterior leaves of the broad ligaments to each other and to the uterus, often to a rather high point on the posterior surface of the uterus. Second, a Baldy-Webster round ligament operation, performed with silk. Third, advancement of the bladder reflexion from its almost invariably low level on the cervix to a more nearly normal location on the fundus.

Such a replacement operation builds a basement of support for the uterus from the uterosacrals and posterior leaves of the broad ligaments. The Baldy-Webster technic is not only of great value in maintaining an anterior position

of the uterus but also tends to correct the commonly associated prolapse of the ovaries. Sometimes the uteroovarian ligaments are still so attenuated that further shortening is necessary; this is accomplished by angleworm reefing with silk. Advancement of the reflexion of the bladder is important in keeping the uterus forward. When a tube or a tube and ovary have to be removed, or if the round ligaments are not markedly attenuated, we sometimes substitute an *angleworm reefing of the round ligaments*, with silk, for the preferred Baldy-Webster technic.

Sixty-nine patients (48 per cent) were subjected to reconstructive replacement operations; 47 were classical replacements and 22 included reefing of the round ligaments.

*Destructive Abdominal Operations.*—Defundation, with suturing of the uterosacrals and posterior leaves of the broad ligaments together with advancement of the bladder, has been employed when further pregnancies were impossible or inadvisable, and a preservation of regular menstruation was desired. Removal of the fundus was resorted to fifteen times.

Thirty-two patients were subjected to supravaginal and eight to complete hysterectomy. The uterosacral ligaments were frequently sutured together and to the cervix after a supravaginal hysterectomy.

Many of the patients in these abdominal cases were also operated upon vaginally, for repair of a cystocele, lacerated perineum and rectocele, or an unhealthy cervix. If the vaginal work includes correction of a cystocele, the usual advancement of the bladder reflexion within the abdomen is omitted not only because it is unnecessary but it also may increase the incidence of infection.

*Vaginal Operations.*—Vaginal operations alone were performed twenty-one times but only for *incidental* displacement of the uterus. Extensive plastic procedures were necessary for most of these cases. There were 9 vaginal hysterectomies; 6 patients were curetted for diagnosis and the menopause was induced in 5 with radium and in one with x-ray; in 5 the Watkins' interposition operation was the procedure of choice (twice after vaginal defundation); and in only one did the technic include transfer of the bases of the broad ligaments.

## RESULTS

One hundred twenty-one patients (85 per cent) have obtained complete symptomatic relief and an excellent clinical result; 4 have failed to report for examination; and 2 died, both from pulmonary embolism. Seven have slight sagging of the uterus, 2 of these followed subsequent deliveries, *but in not a single patient has the uterus returned to a retrodisplaced position.* Four have small cystic adnexal tumor masses which cause moderate discomfort; 3 of these occurred in patients with residues of pelvic infection; 1 followed a supravaginal hysterectomy; and 2 occurred after defundation attended by a febrile convalescence. Two patients with endometriosis, subjected to a conservative reconstruction type of operation, continue to have marked dysmenorrhea and some bleeding; 2, with pelvic residues, developed postoperative cystic tumor masses and had to be reoperated. One patient has residual thrombophlebitis although the pelvic symptoms, for which she was operated,

have been completely relieved; another complains of pelvic pain, apparently the result of postoperative adhesions which followed a previous operation; one continues to menstruate twice a month but the uterus is in excellent position.

Nineteen patients complained of sterility but 3 were found to have had the tubes removed at a previous operation. In 7 it was necessary to perform a destructive type of operation, not compatible with subsequent conception. Nine reconstructive operations were attempted and 2 of these patients have subsequently been delivered of healthy babies.

Eleven women became pregnant following replacement operations, but we have had an opportunity, thus far, to examine only 3 of these patients after delivery; one has a perfect anatomic result, in the other two there is a slight tendency to sagging of the uterus (both were reefing cases). However, obstetricians tell me that the classical abdominal replacement operation which we advocate does not interfere with the normal progress of labor and the uterus returns to its anterior position following delivery.

*Additional Data.*—In six patients an acutely inflamed appendix was found at operation; in only 2 was there a preoperative diagnosis of *acute appendicitis;* the others were unsuspected findings.

*Adhesions of the anterior surface of the liver* were found six times. Massive adhesions were encountered in the patient with tuberculous salpingitis. Five, with gonorrheal tubal disease, had typical adhesion bands of the anterior surface of the liver. Such adhesions, as described by Dr. Curtis, are found so frequently in patients with gonorrheal tubal disease that we consider their presence almost pathognomonic of a preexistent gonorrheal pelvic infection.

Of 17 patients subjected to *defundation,* 15 were operated upon by the abdominal route and 2 vaginally; 1 of the vaginal cases developed a large pelvic abscess which was drained. Only 7 of the abdominal defundations pursued a normal postoperative course; 5 were febrile; 1 had a pulmonary embolus and 2 developed infected wounds.

Of 22 patients in whom replacement of the uterus included a *reefing of the round ligaments,* 16 are known to have obtained a good result; 1 failed to report for examination; in 5 (23 per cent) there is some sagging of the uterus.

Only 4 patients with retroflexion had had the *cervix cauterized* prior to their abdominal operation. In 2 there was no history of pelvic infection and no evidence of it was found at operation; in the other 2, however, adhesions and scar tissue encountered at operation confirmed our impression that endocervical cauterization of a markedly retrodisplaced uterus is inadvisable.

Five women with retrodisplacement and menopausal bleeding were subjected to diagnostic curettage and intrauterine radiation (1200 to 2000 mc.); none of this group developed pelvic infection.

## CONCLUSIONS

1. Retrodisplacement of the uterus per se may be responsible for lower abdominal and pelvic discomfort, uterine bleeding and dysmenorrhea; these symptoms are amenable to relief by operative intervention.

2. The findings at operation indicate that retrodisplacement of the uterus is a menace to the health of the ovaries and is responsible for the development of large, edematous, cystic ovaries which function abnormally; and equally important, retrodisplacement apparently predisposes to endometriosis and perhaps to uterine fibroids.

3. The operative replacement of a symptomless, large, heavy, dragging retroflexed uterus, in younger women, is *sometimes* a justifiable procedure as a prophylactic measure.

4. In this series retrodisplacement was an infrequent cause of backache; it alone was not responsible for sterility and apparently did not increase, materially, the incidence of spontaneous abortions.

5. The surgical correction of retrodisplacement should embrace a utilization of all supporting structures, namely the uterosacral ligaments, the posterior leaves of the broad ligaments, the round ligaments, and the peritoneal reflexion of the bladder.

6. A recurrence of the retrodisplacement has not occurred in this series after subsequent pregnancies nor has there been any interference with the normal progress of labor.

7. Substitution, in selected cases, of an angleworm reefing of the round ligaments for the Baldy-Webster technic is helpful, but it is not an ideal procedure.

8. Defundation, employed in the cure of retrodisplacement, is followed by postoperative complications more frequently than is supravaginal hysterectomy.

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Note.—Four other papers presented at this meeting, those of Drs. Healy, Bonney, Caldwell, and J. M. Hundley, Jr., will be included in the November issue, together with the first installment of the discussions.

# Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

## Selected Abstracts

### Radiography and Radiotherapy

**Heyrowsky, K.: When Is an X-Ray Picture Indicated in Obstetrics?** Med. Klin. **30:** 1630, 1934.

Obstetricians should resort to x-ray to clear up any indefinite situation. When complications are due to pelvic contraction an x-ray picture will indicate whether or not a patient should be delivered in a hospital or at home. The x-ray will demonstrate anomalies in the shape of the pelvis. The author emphasizes that clinical measurements are by no means as reliable as the measurements obtained by means of x-ray plates. X-ray pictures of lateral views are most helpful and are absolutely indicated in all cases of contracted pelvis, funnel pelvis, and spondylolisthesis. In cases of abnormal presentation and deflection attitude, a correct diagnosis can easily be made by means of x-ray pictures. Furthermore, the x-ray will verify a diagnosis of multiple pregnancy, monsters and a suspicion of intrauterine death of the fetus.

The author does not believe in the use of x-ray pictures for the purpose of measuring the fetal head, because thus far none of the methods advocated for this purpose have proved practical. He emphasizes particularly that chief reliance in obstetric difficulties should be placed upon clinical examination, and that x-ray pictures should be the last resort. In the vast majority of cases labor may be conducted safely without x-ray pictures. Exposures for x-ray pictures have absolutely no harmful effect upon the baby.

J. P. GREENHILL.

**Wahl, F. A.: Roentgenology in Obstetrics,** Arch. f. Gynäk. **152:** 173, 1933.

Roentgenology provides valuable assistance in obstetrics in those instances in which physical and clinical examinations do not reveal all of the necessary information. Many cases which are obscure from a diagnostic point of view are cleared up by roentgenographic studies. The location and position of the fetus, station of the presenting part, and the relationship between head and pelvis and multiple pregnancies are clearly shown on x-ray plates. It is the most accurate method of determining malformation or death in utero. It should never be omitted as a safeguard before cesarean section. At times a single plate will not give all the necessary data but the author warns against repeated films on account of possible danger to the fetus.

RALPH A. REIS.

**Hajkis, Miron: Radiographic Evidence of Live Birth,** Lancet 2: 134, 1934.

The author states that the radiographic evidence of air in the lungs and the duodenum is strong proof of live birth. Air may be blown into the stomach by mouth-to-mouth breathing but not into the duodenum. He also remarks that the lungs of stillborn infants could not be inflated artificially.

Atelectasis is most pronounced in the bases of the lungs, and more in the left than the right.

This procedure is of medicolegal import, even realizing that putrefaction may produce gas but this will be as bubbles and not as air-filled alveoli or bowel.

H. CLOSE HESSELTINE.

**Béclère, C.: Metrorrhagia Among Young Women,** Bull. Soc. d'obst. et de gynéc. p. 688, 1934.

Béclère has observed 70 cases of metrorrhagia in young women where the etiology was unknown. In such cases he has employed hysterosalpingography and believes this to be the best means of exploration of the uterus. It is simple, rapid, and without danger. It is the only means of detecting a beginning cystic salpingitis. It likewise reveals intrauterine lesions such as retention of placental tissue, polyps, submucous fibroids, and cancer of the body of the uterus. It also gives information concerning lesions of the tubes. If hysterography is performed systematically it will permit limitation of curettement to those cases where there exists an intrauterine lesion. Curettement will then be necessary in only one-eighth of all cases of metrorrhagia in young women. The author points out that chronic infection of the genitalia is a frequent cause of bleeding because he found infection in two-thirds of his cases. Hence, treatment should be directed against infection. Patients with cystic salpingitis should be operated upon and the others treated by means of vaccines and medical diathermy.

J. P. GREENHILL.

**Jarcho, J.: The Value of the Roentgen Ray in Gynecology,** Am. J. Surg. 21: 13, 1933.

Uterosalpingography is of the utmost importance: (1) in establishing the patency or nonpatency of fallopian tubes and definitely locating the site of blockage in cases of occlusion; (2) in restoring the patency of occluded tubes; (3) in suggesting the best site for a stoma in operations on sealed tubes or indicating the part of the tube to be resected; (4) in determining the success of salpingostomy and preventing the stoma from contracting and closing secondarily; (5) in the diagnosis, prognosis, and treatment of chronically inflamed and occluded tubes; (6) in deciding in cases of fibroid of the uterus upon the most advisable therapeutic procedure, whether surgical interference, roentgen, or radium treatment; (7) in making a differential diagnosis, in settling differences of opinion in pelvic diagnosis, and in providing a permanent record for future use.

J. THORNWELL WITHERSPOON.

**Béclère, C.: Accidental Vascular Injection in the Course of Hysterosalpingography,** Bull. Soc. d'obst. et de gynéc. p. 31, 1933.

In 1926 Béclère published two reprints of roentgen ray pictures which demonstrated the injection of iodized oil into blood vessels during experimental work. At that time he cautioned against the use of excessive pressure in the instillation of lipiodol. In 1929 Brull, Vaurell and Riera demonstrated the accidental injection of

lipiodol into blood vessels in a woman. (Since then other reports of this accident have appeared, J. P. G.) Béclère says that he has not infrequently detected such accidents in the published pictures of other authors who did not recognize the complication and assumed the shadows indicated tubal permeability. Hence this accident is more common than is generally believed.

Vascular injection of lipiodol can occur only if both tubes are obstructed. The day after the injection, the iodized oil has escaped into the general circulation and cannot be found in the pelvis.

The accident occurs (1) when too much pressure is exerted in the presence of closed tubes, (2) when the uterine cavity is very small in cases of underdevelopment and the tubes are sealed off, and (3) where salpingectomy has been performed and there are abnormal vascular anastomoses. On the other hand, it is rare in cases of metrorrhagia. Fortunately accidental injection of lipiodol is well tolerated by the patient.

J. P. GREENHILL.

**Shute, E., and Davis, M. E.: Histologic Changes in Rabbits and in Dogs Following the Intravenous Injection of Thorium Preparations,** Arch. Path. **15**: 27, 1933.

By means of intravenous injection of colloidal preparations of thorium, viz: tordiol, umbrathor and the less toxic thorotrast, Shute and Davis were able to secure visualization of the liver and spleen in rabbits and dogs but were unable to visualize the placenta. These authors used smaller doses than did others for successful placental visualization in the rat. Even their smaller dosages produced intense degeneration of the liver and spleen and caused one rabbit to abort and to have a spontaneous rupture of the spleen and a postpartum hemorrhage. They state that colloidal thorium has no place in clinical work.

Particles of thorotrast practically disappear from the liver and spleen in two or three months after injection, and the cells regain an almost normal appearance. The placenta of the dog and of the rabbit appears to be an effective barrier to the transmission of thorium to the fetus. With the exception of the animal mentioned, all of their pregnant animals carried their young to term or were killed near term for study. The metal could be found in the rabbit placenta microscopically up to eleven days after injection, but by this time it was in the form of very fine particles and after that seemed to disappear. Placental cells do not show the destructive changes observed in the cells of the liver and spleen.

W. B. SERBIN.

**Gilbert, P.: Radiotherapy of Tuberculous Adnexitis,** Bull. Soc. d'obst. et de gynéc. p. 606, 1933.

The tubes are involved in 80 to 90 per cent of all cases of tuberculosis of the female genital tract. The diagnosis is difficult to make before operation and even at operation it is impossible to recognize the true diagnosis in most cases. Microscopic examination is necessary.

The indications for radiotherapy in this condition depend upon the age of the patient and the severity of the lesions. In young women radiotherapy should be used only if change of climate, heliotherapy and ultraviolet rays have failed. Even in apparently hopeless cases, radiotherapy should be tried. The action of the roentgen rays is not directly on the tubercle bacilli but upon the tubercles which are radiosensitive. In serious cases, all ovarian function should be eliminated.

Gilbert treated 13 women who had tuberculous salpingitis with roentgen rays. In 9 cases there was a clinical cure, in 5 cases there was considerable amelioration and 3 women died of a continuation of the tuberculous process.

J. P. GREENHILL.

**Jacobi, H., and Lindner, J.: Indications, Results and Failures of Roentgen Ray Castration,** Monatsch. f. Geburtsh. u. Gynäk. **94**: 178, 1933.

From 1928 to 1931 roentgen rays were used for the purpose of producing castration in 383 women. Twelve women could not be traced and 4 died. Among the 367 remaining women, there was an amenorrhea after one or more bleedings in 96.2 per cent of all the cases. If the roentgen rays are applied to the ovaries in the first half of the menstrual cycle, amenorrhea sets in more quickly than if the rays are applied in the second half of the period. Likewise the older the patient, the more quickly will amenorrhea result after radiation. In 14 women (3.8 per cent) an amenorrhea failed to result.

No harmful sequelae were observed after radiation. Forty-one women complained of hot flashes and 35 had palpitation, headaches, and abdominal discomfort.

J. P. GREENHILL.

**Tesauro, G.: Pregnancy After X-Ray Treatment of the Mother,** Ztschr. f. Geburtsh. u. Gynäk. **102**: 522, 1933.

In a series of 68 patients who were subjected to ovarian-stimulating doses of x-ray for various reasons, mainly for amenorrhea and oligomenorrhea, 18 subsequently became pregnant and delivered 21 children. In 5 cases pregnancy occurred within the first year after treatment, in the remaining ones in from one to six years. The x-ray dose was never over 10 per cent of the erythema dose, ranging mainly from 2 to 5 per cent.

All pregnancies and all deliveries ran a normal course. The children were observed over a period of five years. No anomalies of growth or general development were noted. The writer merely states these facts, considering the number of cases too small to warrant conclusions.

GROVER LIESE.

**Husted, E.: On X-Ray Treatment in Certain Forms of Metrorrhagia,** Acta obst. et gynec. Scandinav. **13**: 103, 1933.

Hypertrophia irregularis glandularis endometrii is found chiefly in women near the climacterium, but occurs also in young and relatively young women. It seldom occurs during the menopause.

The endometrial changes are associated with quite irregular, often protracted or profuse hemorrhages which may lead to a marked degree of anemia; in several cases the abnormal hemorrhage is preceded by an interval considerably longer than that of the normal menstrual cycle.

Physical examination of the patient usually reveals no definite abnormality other than some degree of anemia; nor does gynecologic examination as a rule show any abnormality. An abnormal condition of the adnexa is made out only in a very few cases. Hence the diagnosis can be made only by histologic examination of the endometrium, by demonstration of the typical changes. The endometrial changes are very likely to recur after curettage.

X-ray treatment has given excellent results; it has been easy to carry out, and ambulatory treatment was given without any inconvenience in the great majority of the cases reported by Husted. Among 100 patients treated with x-rays who were

examined one to eight years after the treatment, only two had a relapse. In one of these, the condition proved refractory to x-ray treatment requiring operation.

In most of the patients the x-ray treatment was followed by symptoms of ovarian insufficiency, usually of a fairly mild character, giving actual discomfort only in about one-fourth of the cases. These symptoms, on the whole, appear to have been no worse than the average run of such complaints in connection with the normal climacterium.

The conclusions that may be drawn from the material presented as to the treatment of those cases of metrorrhagia in which there is irregular glandular hypertrophy of the endometrium are as follows:

In older patients, near the climacterium, x-ray treatment is indicated when the diagnosis is established by the histologic findings.

In younger patients, in the latter part of the thirties, without beginning symptoms of ovarian insufficiency, the effect of curettage is awaited; if there is a relapse of the condition, x-ray treatment is given, after repeated curettage when required.

Hysterectomy ought to be the ultimate resort to fall back upon only in the extremely rare instances where the hemorrhages cannot be checked by x-ray treatment.

J. P. GREENHILL.

**Vogt, E.: The Roentgen Ray and Radium Treatment of Inoperable Ovarian Carcinoma,** Med. Klin. **29**: 1464, 1933.

The experience of Vogt with the postoperative roentgen ray and radium treatment of inoperable carcinoma of the ovary leads him to conclude that in cases of operable carcinoma of the ovary it is wise to employ postoperative roentgen ray treatment prophylactically. A full dose is administered. In cases of inoperable cancer of the ovary where the diagnosis was proved by exploratory laparotomy and biopsy, the author combines a full roentgen ray dose with 2,000 mgm. hours of intrauterine radium. This is repeated two or three times. Vogt believes that combined roentgen ray and radium therapy gives better results than roentgen ray treatment alone.

J. P. GREENHILL.

**Nielsen, M.: Radium Treatment of Cancer of the Cervix During Pregnancy,** Acta obst. de gynec. Scandinav. **13**: 235, 1934.

Cancer of the cervix is a rare complication in pregnancy (about 0.005 per cent). Whether cancer of the cervix takes a particularly rapid course during pregnancy is a question that cannot be answered generally, but it is a striking fact that the cancer is often inoperable in the latter half of the gestation period when the patient applies for treatment. A report is given of 3 cases of posteonceptional radium-treated cancer of the cervix, together with a review of 41 cases gathered from the literature.

In 12 out of these 44 cases the pregnancy was interrupted by abortion. Among the 32 children who were born at term or nearly so, only 3 were defective as a result of the treatment. Thus the prognosis is relatively good as far as the children are concerned. For the mothers the prognosis is poor, only 8 being alive three years after the treatment. Labor at term or abortion was spontaneous in 32 of these patients; 5 of these died from hemorrhage during parturition, 2 from infection. Operation was performed in 12 cases: Cesarean section in 5 (one with fatal outcome, eclampsia), cesarean section with supravaginal amputation of the uterus in 4 (one died), and cesarean section with total hysterectomy in 4 (all fatal).

Out of regard for the child the author advises against intracervical radium treatment, and, on account of the danger of fatal hemorrhage during parturition at term, cesarean section is recommended, with supravaginal amputation if advisable.

J. P. GREENHILL.

**Porcaro, Diego: Bullettino della Sacreta Piemonteso,** Arch. di ostet. e ginec. 40: 295, 1933.

The author reports his results with x-ray treatment of the pituitary and thyroid glands in women suffering from surgical menopause. The study is based on 11 cases, in which excellent results were obtained in 9. The results on 2 women were negative. The x-ray dose on both the pituitary and thyroid glands was a stimulating one. The blood pressure and pulse rate were recorded. Following the treatment the blood pressure was lowered and the pulse rate slower.

AUGUST F. DARO.

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# Items

## American Board of Obstetrics and Gynecology Examination

The next written examination and review of case histories of Group B applicants for certification by this Board will be held in various cities of the United States and Canada on Saturday, December 7, 1935.

Application blanks and booklet of information may be obtained from Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania. Applications for this examination must be filed in this office not later than November 1, 1935.

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The *Editors* are pleased to announce the resumption in an early issue of the discussions of papers read at the meetings of the various societies of which this JOURNAL is the official organ. It is necessary, in order to conserve space, to condense this material as much as possible, but it is hoped that as published, the discussions will add much to the value of the papers.

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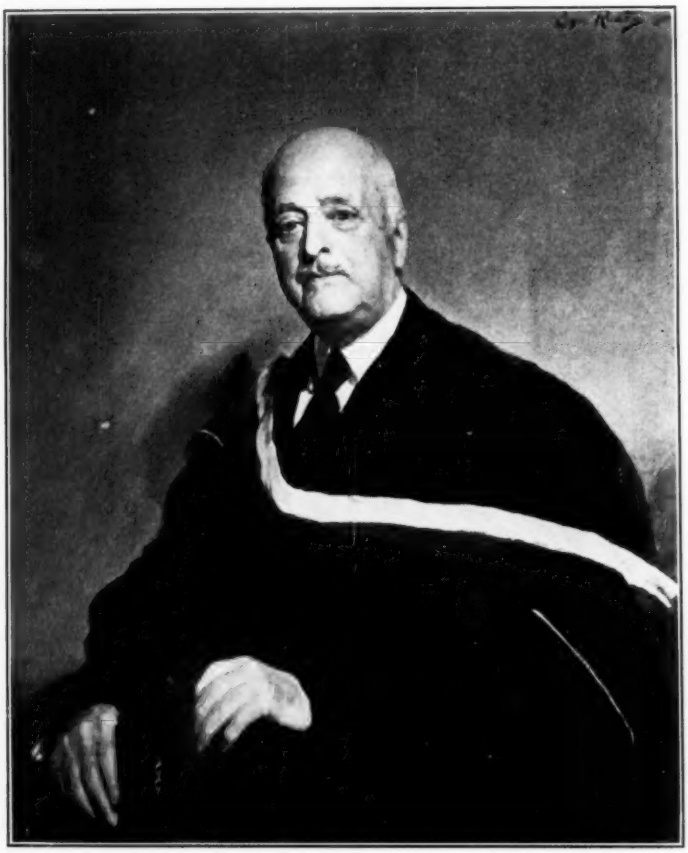
## Erratum

In the article by Drs. Allen and Reynolds in the September issue of the JOURNAL, on page 318, the fifth and sixth lines under "Note" should read: In this paper the B-type crystals of progestin (m.p. 128°) are known now as A *progesterone*, and the C-type crystals of progestin (m.p. 120.5°-121°) are now known as B *progesterone*.



BARTON COOKE HIRST 1861—1935